

1 FOOD AND DRUG ADMINISTRATION

2 CENTER FOR TOBACCO PRODUCTS

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6 TOBACCO PRODUCTS CONSTITUENTS SUBCOMMITTEE
7 TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

8
9 WEDNESDAY, JUNE 9, 2010

10 8:00 a.m. to 2:30 p.m.

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14 Holiday Inn
15 2 Montgomery Village Avenue
16 Gaithersburg, Maryland
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P R O C E E D I N G S

(8:00 a.m.)

DR. HATSUKAMI: All right. It's a little past 8:00 a.m., so I think we'll go ahead and get started. I'm Dorothy Hatsukami. I'm serving as chair of this subcommittee meeting. So good morning to everyone and thank you for joining us today.

I want to make a few statements, and then we're going to introduce the committee members again, committee members and consultants.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act,

1 we ask that the advisory committee members take care
2 that their conversations about the topic at hand take
3 place in the open forum of the meeting.

4 We are aware that members of the media are
5 anxious to speak with the FDA about these proceedings.
6 However, FDA will refrain from discussing the details
7 of this meeting with the media until its conclusion.
8 Also, the committee is reminded to please refrain from
9 discussing the meeting topic during breaks or lunch.
10 So thank you.

11 I think we'll go ahead and introduce the
12 committee members and consultants. So we'll start
13 with Dr. Ashley.

14 DR. ASHLEY: David Ashley. I am director of
15 the Office of Science for the Center for Tobacco
16 Products at FDA.

17 DR. HUSTEN: Corinne Husten, senior medical
18 advisor, Center for Tobacco Products, FDA.

19 DR. JINOT: Jennifer Jinot. I'm with the
20 Environmental Protection Agency.

21 DR. HECHT: Steve Hecht. I'm a professor at
22 the Masonic Cancer Center, University of Minnesota.

1 DR. BURNS: Dave Burns, from UCSD.

2 DR. O'CONNOR: Richard O'Connor, from
3 Roswell Park Cancer Institute.

4 DR. TEMPLETON-SOMERS: Karen Templeton-
5 Somers. I'm acting designated federal official for
6 the committee, FDA.

7 DR. HENNINGFIELD: Jack Henningfield, Johns
8 Hopkins University School of Medicine and Pinney &
9 Associates.

10 DR. WATSON: Cliff Watson, research chemist,
11 Centers for Disease Control and Prevention.

12 DR. DJORDJEVIC: Mirjana Djordjevic, project
13 director, project officer, in the Tobacco Control
14 Research Branch, the National Cancer Institute.

15 DR. FARONE: Bill Farone, president and CEO
16 of Applied Power Concepts, Incorporated.

17 DR. LAUTERBACH: John Lauterbach, Lauterbach
18 & Associates, Macon, Georgia, representing the
19 interests of the small business tobacco manufacturers.

20 DR. HECK: Dan Heck, principal scientist at
21 the Lorillard Tobacco Company, representing the
22 interests of the tobacco manufacturers.

1 DR. TEMPLETON-SOMERS: Good morning. I
2 would like to remind everyone present to please
3 silence your cell phones, if you've not already done
4 so. I would also like to identify the FDA press
5 contact, Tesfa Alexander, standing over there.

6 The Food and Drug Administration is
7 convening today's meeting of the Tobacco Product
8 Constituents Subcommittee of the Tobacco Products
9 Scientific Advisory Committee under the authority of
10 the Federal Advisory Committee Act of 1972.

11 With the exception of the industry
12 representatives, all members/consultants are special
13 government employees or regular federal employees from
14 other agencies and are subject to federal conflict of
15 interest laws and regulations.

16 The following information on the status of
17 this subcommittee's compliance with federal ethics and
18 conflict of interest laws covered by, but not limited
19 to, those found at 18 USC Section 208 and Section 712
20 of the Federal Food, Drug, and Cosmetic Act is being
21 provided to participants in today's meeting and to the
22 public.

1 FDA has determined that the members and
2 consultants of this subcommittee are in compliance
3 with federal ethics and conflict of interest laws.
4 Under 18 USC Section 208, Congress has authorized FDA
5 to grant waivers to special government employees and
6 regular federal employees who have potential financial
7 conflicts when it is determined that the agency's need
8 for a particular individual's services outweighs his
9 or her potential financial conflict of interest.

10 Under Section 712 of the FD&C Act, Congress
11 has authorized FDA to grant waivers to special
12 government employees and regular federal employees
13 with potential financial conflicts when necessary to
14 afford the committee essential expertise.

15 Related to the discussions of today's
16 meeting, members and consultants of this committee
17 have been screened for potential financial conflicts
18 of interest of their own, as well as those imputed to
19 them, including those of their spouses or minor
20 children, and, for the purposes of 18 USC Section 208,
21 their employers.

22 These interests may include investments,

1 consulting, expert witness testimony, contracts,
2 grants, CRADAs, teaching, speaking, writing, patents
3 and royalties, and primary employment.

4 Today's agenda involves receiving
5 presentations and discussing the development of the
6 list of harmful or potentially harmful constituents,
7 including smoke constituents, in tobacco products.
8 Topics for discussion will include the criteria for
9 selection of the constituents, developing a proposed
10 list of harmful or potentially harmful constituents,
11 the rationale for including each constituent, and the
12 acceptable analytical methods for assessing the
13 quantity of each constituent.

14 This is a particular matters meeting during
15 which general issues will be discussed. Based on the
16 agenda for today's meeting and all financial interests
17 reported by the committee members and consultants, no
18 conflict of interest waivers have been issued in
19 connection with the meeting.

20 To ensure transparency, we encourage all
21 standing committee members and consultants to disclose
22 any public statements they have made concerning the

1 issues before the committee.

2 With respect to FDA's invited industry
3 representatives, we would like to disclose that Drs.
4 Daniel Heck and John Lauterbach are participating in
5 this meeting as nonvoting industry representatives,
6 acting on behalf of the interests of the tobacco
7 manufacturing industry and the small business tobacco
8 manufacturing industry, respectively.

9 Their role at this meeting is to represent
10 these industries in general, and not any particular
11 company. Dr. Heck is employed by Lorillard Tobacco
12 Company and Dr. Lauterbach is employed by Lauterbach &
13 Associates, LLC.

14 FDA encourages all other participants to
15 advise the committee of any financial relationships
16 that they may have with any firms at issue. Thank
17 you.

18 DR. HATSUKAMI: Thank you. So on our agenda
19 today, we won't have a presentation by Dr. Watson,
20 because he gave his excellent presentation yesterday.
21 And so what we're going to do is we're going to start
22 off with looking at the list of carcinogens that we

1 had developed yesterday.

2 I believe the folks from the FDA have
3 actually provided the list of carcinogens that were
4 determined using the IARC criteria, but then, also,
5 other carcinogens that had been identified using other
6 criteria.

7 So we're going to go through that list to
8 determine whether the carcinogens identified by the
9 other criteria have been either included in our list
10 that we discussed yesterday or need to be included.

11 DR. LAUTERBACH: Dr. Hatsukami?

12 DR. HATSUKAMI: Yes, Dr. Lauterbach?

13 DR. LAUTERBACH: When are we going to have a
14 chance for follow-up questions with Dr. Watson?

15 DR. HATSUKAMI: I think maybe the best time
16 to have those questions is when we start discussing
17 some of the methods issues.

18 DR. LAUTERBACH: Okay.

19 DR. HATSUKAMI: Would that be okay with you?

20 DR. LAUTERBACH: Yes. Thank you.

21 DR. HATSUKAMI: All right. So we don't have
22 a copy of the list. So we're going to have to take a

1 look at the list that we have developed right on the
2 screen.

3 DR. HUSTEN: The handout had the full list,
4 with a checkmark around whether they were carcinogens,
5 and this was just defining, as was requested
6 yesterday, which ones are on the IARC list and then
7 which ones were on one of the other lists.

8 In the background materials -- in the
9 background materials, so it's that table. That table.

10 DR. HATSUKAMI: All right. So we'll just go
11 through this. And what I'd like to do is I would
12 actually like to make sure that we captured the non-
13 IARC -- the ones that were not on the IARC list,
14 whether we want to include them in our current list or
15 not.

16 So to start off with, the acetaldehyde and
17 acrylonitrile are ones that we identified. The
18 1-aminonaphthalene is one that was identified by NIOSH
19 that was not -- but that we did include on the list, I
20 guess. And I assume that everybody is in favor of
21 that.

22 All right. Let's just go down, because I

1 think we don't need to go over the ones that are on
2 the IARC list. Okay. We decided to include the
3 cresols, which was not on the IARC list, but which was
4 identified by EPA.

5 Crotonaldehyde, also, we included. It was
6 on the EPA list and not the IARC list. Hydroquinone
7 we decided to include, but it was not on the IARC list
8 and it was not on any other list.

9 Is that right? Okay.

10 Is that something that the committee does
11 want to include?

12 [No response.]

13 DR. HATSUKAMI: Any objections? Okay.

14 Mercury, it was on the IARC list in 1993.

15 DR. HUSTEN: That's correct, methylmercury.

16 DR. HATSUKAMI: I'm sorry. Methylmercury
17 was included on the IARC list in 1993. And I guess
18 the question is whether we want to include mercury.
19 Yes?

20 DR. HECHT: It's not methylmercury in
21 tobacco smoke, is there, or tobacco?

22 DR. HATSUKAMI: There's no methylmercury in

1 tobacco smoke?

2 DR. HECHT: I don't know. I don't know.

3 But I'm not aware of -- does anybody know if there's
4 methylmercury in tobacco? I mean, we shouldn't have
5 things on the list that aren't present.

6 DR. HATSUKAMI: Absolutely.

7 DR. HECHT: That would look stupid.

8 DR. HATSUKAMI: Yes, Dr. Lauterbach?

9 DR. LAUTERBACH: Most of the work over the
10 years has been done on inorganics in tobacco, looking
11 at the metals. People have not looked at balance
12 state or organometallics. So I couldn't honestly
13 answer that question either yes or no.

14 DR. HATSUKAMI: So if nobody knows for sure,
15 then it should not be on the list.

16 Is that what I'm hearing?

17 DR. HECHT: Correct. Right.

18 DR. HATSUKAMI: Okay. Any objection?

19 [No response.]

20 DR. HECHT: Otherwise, the list is going to
21 look stupid if we put all kinds of things on there
22 that we don't even know are in the product.

1 DR. HATSUKAMI: N-nitrosoanabasine, we
2 included. It was on the IARC list 2007, limited
3 evidence of carcinogenesis in experimental animals.
4 It should say not classifiable in humans.

5 So is that something that we do not want to
6 include? We do want to include, okay.

7 Any objections to that?

8 [No response.]

9 DR. HATSUKAMI: Okay. The phenol we decided
10 not to include as a carcinogen. The quinoline, it
11 says likely to be a carcinogen in humans, determined
12 by the EPA.

13 Is that what we want to include? Okay.

14 Tar produces as carcinoma when -- and what
15 was the -- I guess that doesn't have to be a source
16 for that.

17 So do we want to include tar? Any
18 objections to including tar?

19 [No response.]

20 DR. HATSUKAMI: No. Steve?

21 DR. HECHT: I don't object, but I'd like to
22 go back to this thing I brought up yesterday of the

1 possibility of including subfractions of tar. Maybe
2 we should discuss that.

3 If we're including tar, tar is a mixture.
4 But there are subfractions of tar that are known to
5 have activity and there are other subfractions that
6 don't. So it's not a pretty thing to analyze for.

7 But should we include it? I just think we
8 should discuss it.

9 Does anybody have an opinion on it?

10 DR. HATSUKAMI: Subfractions of tar. Sure.

11 Dr. Lauterbach?

12 DR. LAUTERBACH: I take your point,
13 Dr. Hecht, and I appreciate your knowledge of the
14 older tobacco literature, but we have, I guess, 1,500-
15 2,000 brand styles that may have to get analyzed, and
16 I'm not sure if we can get them through the
17 laboratory, whether there's people in Center for
18 Tobacco Products, just some numbers and skills,
19 analyze the data that's going to be coming in.

20 It may be we need to be more judicious in
21 our selection of the analytes to be required for the
22 different cigarette smoke samples that are submitted.

1 DR. HATSUKAMI: Do you have a response to
2 him?

3 Yes, Dr. Burns?

4 DR. BURNS: Well, at least in my mind, the
5 purpose of including tar is not only that it is a
6 carcinogen, but that it provides a means of
7 normalizing the rest of the constituents that are
8 measured to something that allows comparison across
9 brands in a meaningful way.

10 I think to the extent that the information
11 provided with the individual constituents doesn't
12 fulfill the needs of the FDA to monitor what's
13 happening or we identify efficiencies from using some
14 kind of subfraction, then it certainly would make
15 sense to consider adding subfractions. But I'm not
16 sure we have that at this point in time.

17 I don't think we have a clear reason at this
18 point in time why that would add something that isn't
19 present from the individual constituents on the list.

20 DR. HECHT: We do, for purposes -- some of
21 the subfractions have activity, but we don't know
22 what's responsible for the activity. For example, the

1 weak acidic fraction has tumor-promoting activity, but
2 we don't know what's responsible for it. So that
3 would be the reason to do it.

4 DR. BURNS: I appreciate that. I'm sort of
5 less excited about generating information that we
6 don't know what to do with. But nevertheless, what
7 I'm saying, basically, is at the point in time at
8 which the information provided can be linked to some
9 concept or some action that is of value to the FDA
10 going forward, then I think it would make great sense.

11 DR. HATSUKAMI: I think maybe for this
12 initial list, it would be fine to include tar and
13 maybe in the future, subfractions can be considered.

14 Dr. Heck?

15 DR. HECK: I think maybe one fortunate thing
16 with the advance of the toxicological science is in
17 terms of tobacco smoke and smoke condensates. The
18 original fractionation schemes at Hoffman and that
19 Dr. Hecht is familiar with were all developed around
20 the older mouse skin painting bioassays.

21 We now, I think, have a better understanding
22 of the potential chemistry of the possible tumor-

1 promoting fractions in smoke. I think we've captured
2 a lot of the -- like the hydroquinone, quinine, a lot
3 of the -- some of the chemical entities that are
4 probably involved in chronic inflammatory processes
5 that may likely be the drivers of that promoting
6 effect that Dr. Hecht described.

7 So we may have a scheme already here to
8 capture that activity, as we understand it, at least
9 in a general way, these days.

10 DR. HATSUKAMI: Okay. So I think the
11 consensus is we should take a look at tar, but not the
12 subfractions of tar today, at this point in time. All
13 right. And I think that's our list, and then we have
14 all the other constituents that we had talked about
15 yesterday.

16 Anymore additional constituents to consider?

17 DR. HECHT: Are we going to review this list
18 now and make sure that we got everything from the IARC
19 list?

20 DR. HATSUKAMI: I think we had the list
21 yesterday. But did you want to review it again?

22 DR. HECHT: I don't know. Maybe you've

1 already done so.

2 DR. HATSUKAMI: Well, if you'd like to go
3 through the list, the ones that you had recommended
4 yesterday --

5 Is that right? Is that what you want to go
6 through?

7 DR. HECHT: I just think that we should have
8 everything on the list that's on this list that I
9 have. If that's been done, then --

10 DR. HATSUKAMI: Yes. It's been done. If
11 you want to just --

12 DR. HECHT: We don't have to waste time
13 going through it.

14 DR. HATSUKAMI: All right.

15 DR. HECHT: You've got the list.

16 DR. HATSUKAMI: It is on the list, yes. The
17 audience has not seen it. Okay.

18 I'm sorry. Dr. Husten?

19 DR. HUSTEN: Well, everything that was on
20 the example list was checked against the IARC list.
21 Everything yesterday that people said to add was
22 added. I do believe there were one or two substances

1 on the IARC list that are not on this list anywhere,
2 because when I was going through and --

3 DR. HECHT: I'm not sure I follow. Which
4 list are you talking about?

5 DR. HUSTEN: So everything on the example
6 list we checked against the IARC list. Yesterday, the
7 group said we want to add these, which are all
8 included. They're at the end, but they're all
9 included.

10 I can't tell -- I think if you compared the
11 IARC list, you might find one or two that are on that
12 list that are not on this list.

13 DR. HATSUKAMI: Has that been identified in
14 this list, the ones that were not --

15 DR. HUSTEN: Not on that list. Let me see
16 if I can find my notes from last night and if I have
17 it, I can tell you quickly what they were. It was
18 only one or two, but I think there were one or two.

19 DR. HATSUKAMI: So meanwhile --

20 DR. BURNS: There were a couple where we
21 weren't sure they were present in tobacco.

22 DR. HATSUKAMI: That's right. I remember

1 that. But meanwhile, I think while Dr. Husten is
2 looking for the two that we excluded, then we should -
3 - Karen had informed me we should let the public know
4 what the other constituents were that we had
5 identified for the list.

6 DR. HUSTEN: So the ones that were on the
7 IARC list that I did not see on the list, one of them
8 was ethylbenzene, which is a 2B categorization. There
9 were several of the N-nitrosamines that were not on
10 there. And excuse me if I do not pronounce these
11 correctly, I'm not a chemist or toxicologist, but N-
12 nitrosomethylethylamine, N-nitrosodiethylamine, N-
13 nitrosopiperidine, N-nitrosodiethanolamine, all of
14 those are 2B, as well, and they were not on this list.
15 2-naphthalene is -- I didn't see it, but it might --
16 this just says 2-naphthalene.

17 That's right. I'm sorry. I didn't realize
18 that was the same as another one. It is on there.

19 Thank you, Patricia.

20 Caffeic acid is a 2B, and the rest are on
21 there.

22 DR. HECHT: I think we should include them

1 all, because I think it's a little arbitrary not to.
2 If our rationale is to include all 2A, 2B and 1, then
3 I don't think we should exclude any at this point.

4 Later on, for example, the nitrosamines that
5 were just mentioned, they will be analyzed, most of
6 them, in the same analysis as dimethylnitrosamine. So
7 if it turns out that they're not there, then they can
8 be deleted. But I think for consistency, we should
9 include everything.

10 DR. HATSUKAMI: Okay. Dr. Burns, do you
11 have a comment?

12 DR. BURNS: I don't disagree with that, in
13 principle, but if, as we went through that list, IARC
14 does it as a carcinogen in the general environment and
15 if the item on that list is not something we have
16 confidence is present in cigarette smoke at this point
17 in time, then I think they should not be included on
18 the list. And there were several, as I recall, that
19 met that criteria.

20 DR. HECHT: There are mixed data in the
21 literature. For example, nitrosopiperidine has been
22 reported a few times, but it's not commonly detected

1 or even analyzed for. So you can't say for sure that
2 it's not present.

3 I don't know what you want to do, but there
4 will be -- after the analytical methods are
5 established, I think that there will be things that
6 will drop off the list, because they've been reported
7 at one time, but possibly they're not present anymore.

8 Maybe the old analyses were wrong. But
9 maybe there is a small amount of nitrosopiperidine in
10 smoke. So if that's the case, we shouldn't exclude it,
11 because it doesn't require its own analysis. It would
12 be found in the analysis of all the nitrosamines
13 anyhow.

14 DR. HATSUKAMI: So, Dr. Hecht, you're saying
15 that we should be comprehensive in terms of our list
16 and it could be -- some of these constituents can be
17 dropped once we get --

18 DR. HECHT: Yes. I think we should be
19 comprehensive and we should be consistent. I don't
20 think we should make decisions sitting here about what
21 may or may not be present, unless it's something like
22 methylmercury, where we're sure that there's no data

1 out there. I think we're sure.

2 DR. HATSUKAMI: Dr. Lauterbach?

3 DR. LAUTERBACH: Let Dr. Heck answer the
4 question here.

5 DR. HECK: If the intent here is to
6 incorporate by reference the entire IARC list of
7 substances purportedly present in smoke, we can do
8 that with the stroke of a pen, but let us be open to
9 the possibility Dr. Hecht has mentioned that some of
10 these may have been based on and, in fact, are based
11 on older chemistry, older methods, older tobacco.

12 There's the nitrosodiethanolamine that was
13 mentioned. This was believed to be a product of an
14 agro-chemical that was used formerly on tobacco. It's
15 not used any longer. So that may be of kind of
16 historical interest, an example of one of those.

17 So as long as we are open to striking a few
18 off the list that do seem irrelevant, we could
19 incorporate it by reference and we're done.

20 DR. HATSUKAMI: Okay.

21 Dr. Lauterbach?

22 DR. LAUTERBACH: I just wanted to follow-up.

1 It's one thing to have these things, but there are
2 laboratories out there that, if these are on the list,
3 they're going to have to go through the cost of method
4 development for analytes they are currently not
5 measuring, and that cost is going to be borne by the
6 consumers of those services.

7 So I think we need to be very judicious in
8 the compounds we put on the list.

9 DR. HATSUKAMI: Dr. Farone?

10 DR. FARONE: These, of course, got on this
11 list because at least once they were found in tobacco
12 smoke. That's what their table says. And the comment
13 that Dr. Hecht made about no longer using a particular
14 chemical.

15 With much of our tobacco being imported from
16 outside the United States, I'm not sure that we even
17 know what's used. And if it's on a list like this,
18 where it's been found before, it seems that Dr.
19 Hecht's explanation that if they're all coming out of
20 the same nitrosamine analysis, I think we just include
21 them all.

22 I did check on the Rodgman/Perfetti list and

1 there is no mention of the methylmercury. So that
2 would be the last place I would know to find a
3 reference for that.

4 But these all at least have been found once
5 or twice, and even though they are from old chemistry,
6 that doesn't mean it was necessarily bad. So I think
7 we need to be careful.

8 DR. HATSUKAMI: Okay. So it seems like the
9 consensus is that we include everything on the list,
10 except for methylmercury, and that we are going to be
11 open to having this list change as we do the analysis.
12 And there may be some that aren't even detectable
13 that, in the future, that they could be dropped, if
14 that's the case.

15 Dr. Burns?

16 DR. BURNS: I would agree with that, but I
17 think we need a preface then to the list that explains
18 what we're doing rather than implying that we have
19 confidence that we know that each of these things are
20 significantly present in tobacco smoke currently.

21 So we ought to explain that that's what we
22 did; in order to be conservative and in order to have

1 a comprehensive list, we have included everything that
2 is hazardous that has been identified, with the
3 understanding that all of these compounds may not
4 still be present in tobacco smoke.

5 DR. HATSUKAMI: Okay.

6 Dr. Hecht?

7 DR. HECHT: I've got footnote B in the list
8 that I gave you that indicates all the compounds that
9 are not routinely analyzed and may not actually be
10 present in current products.

11 DR. HATSUKAMI: Okay. That should be noted.

12 Thank you.

13 Any other comments? Dr. Farone?

14 DR. FARONE: Yes. And that's the same
15 comment that's actually made in the IARC on their
16 list; not commonly reported values may be estimates or
17 unreliable for the smoke of current cigarettes.
18 That's what Steve had on his list, and if we put that,
19 they're all designated in the list with B and there's
20 another footnote A -- if we just are going to include
21 much of these, I think we ought to include the
22 footnotes exactly as they exist here, because it also

1 defines what the complex chemicals are, so that we
2 don't have to write those out.

3 DR. HATSUKAMI: We can note that. All
4 right.

5 Any other comments? Do we have our list of
6 carcinogens then?

7 Okay, good. All right. So let's move on.

8 We're going to have a presentation on
9 methods or criteria that have been used to identify
10 other toxicants, I believe.

11 Dr. Richter will be doing the presentation.

12 DR. RICHTER: Good morning. My name is
13 Patricia Richter. I'm with the Office on Smoking and
14 Health at the Centers for Disease Control and
15 Prevention.

16 There has been discussion about criteria
17 used for designating toxicants in non-neoplastic
18 disease categories, and I'd like to briefly review
19 some of the summary documents that have been prepared
20 by various organizations, in this case, all within the
21 government, that are useful in evaluating a summary of
22 literature, toxicologic literature, exposure

1 literature, in order to make a designation of
2 something as a pulmonary toxicant, a cardiovascular
3 toxicant, or a developmental toxicant, in this case.

4 The first source I'd like to describe is the
5 ATSDR toxicological profiles. These are produced
6 under a congressional mandate to evaluate substances
7 encountered at hazardous waste sites. And the goals
8 of the profiles -- the goal is to identify individual
9 substances in combinations that pose the greatest
10 public health hazard and hazardous waste sites.

11 These are quite comprehensive documents.
12 They're assembled based on a weight of evidence
13 approach, incorporating a variety of human exposure
14 data -- occupational; epidemiological; occasionally,
15 case reports.

16 It attempts a thorough review of animal
17 toxicity studies and both genotoxicity and
18 toxicokinetics data. And they go through an extensive
19 peer review process. They are produced in a way that
20 they can be generated as a draft and sent out for
21 public comment after announcement in the Federal
22 Register.

1 There's typically extensive comment received
2 from interested industries, as these are environmental
3 pollutants, and there is an attempt to incorporate
4 comments, and then they are finalized and republished
5 after a 90-day period. I think that there are over
6 200 of them to date so far.

7 Also, another attempt at reviewing
8 pollutants is a methodology employed by the NIOSH in
9 the CDC, where they develop a criterion for
10 recommending standards of workplace exposure, and a
11 similar weight of evidence approach is employed.
12 There is extensive use of human exposure data in this
13 case, incorporating not only human exposure case
14 reports and experimental data, but also a vast amount
15 of historical data.

16 As with the ATSDR toxicological profiles, it
17 incorporates animal toxicity studies and looks for a
18 correlation between exposure and effect.

19 We had some discussion yesterday, but here
20 is a bit more information on the Environmental
21 Protection Agency methodology. Many of their reviews
22 are available within the Integrated Risk Information

1 System database, IRIS, and the goal of their process
2 is an evaluation of quantitative and qualitative risk
3 information on effects that may result from exposure
4 to environmental contaminants.

5 As with the other two, they employ a weight
6 of evidence approach, incorporating human
7 epidemiological data and providing extensive
8 documentation on long-term experimental animal
9 bioassays. And they also incorporate in some of the
10 decision-making other key data, such as the
11 physical/chemical properties of a chemical,
12 structure/activity relationships. They look at
13 comparative metabolism and toxicokinetic data and mode
14 of action.

15 Relevant to the activities today and for
16 this subcommittee, we've also looked at the California
17 Environmental Protection Agency methodology, which is
18 a process whereby they review chemicals for the
19 potential to act as a carcinogen or a reproductive
20 toxicant. They look not only at developmental
21 endpoints, but, also, reproductive toxicity endpoints.

22 It is based on -- chemicals are recommended

1 by state experts and they typically assemble a
2 subcommittee to review the data and to provide
3 recommendations, and the data are assembled and
4 available in a compiled state, including the
5 discussion that goes with the classifications.

6 This activity is required by law in the
7 state of California for the purpose of labeling
8 chemicals as either a carcinogen or a reproductive
9 toxicant.

10 DR. HATSUKAMI: Questions from the
11 committee?

12 Jennifer?

13 DR. JINOT: I'll just add. You mentioned
14 for ATSDR about the external peer review and the
15 public review process. That also applies to U.S. EPA
16 documents, as well as Cal/EPA, I believe. I don't
17 know the NIOSH process, but the other two definitely
18 have external peer review, also.

19 DR. HATSUKAMI: Any other questions?

20 [No response.]

21 DR. HATSUKAMI: So my question is, we did
22 receive a list of toxicants; that was summarized and I

1 guess we're -- yes. This was provided in the
2 background material.

3 My question to you folks is the list that
4 was compiled for us in the background material, what
5 were the criteria that were used to identify these
6 basic toxicants?

7 DR. HUSTEN: Well, these are the compounds
8 that were on the example lists, across the example
9 lists, and what was done was to then look at these
10 various data sources and see if there was information
11 about the chemicals and if not, were there studies.

12 The first step was to see if any of these
13 agencies had classified these in a certain way or
14 identified certain outcomes based on their reviews.
15 If not, then there was an attempt to go to the
16 literature and see if there were studies about it,
17 especially around respiratory effects or
18 cardiovascular effects.

19 DR. HATSUKAMI: I see. Okay.

20 So how would the committee like to proceed?
21 We have this list that was compiled for us. Some of
22 them are based upon just literature reviews. Some of

1 it is based upon different agencies identifying them
2 as other toxicants, toxicants that are not related to
3 cancer, but to cardiovascular disease and respiratory
4 disease.

5 Would the committee like to go through this
6 list and decide what toxicants we would like to
7 include or is there another process that --

8 Dr. Burns?

9 DR. BURNS: Well, I think it would be useful
10 to go through the list, but I would subtract from the
11 list, at the start, all of the ones that we have
12 already included.

13 DR. HATSUKAMI: Absolutely.

14 DR. BURNS: If we've already put them on the
15 list, there's no point in putting them on twice or
16 having a discussion about them.

17 DR. HATSUKAMI: Right.

18 So the list is on the screen there. So the
19 acetaldehyde we've already included as a carcinogen.

20 Acetone? And it is considered to be
21 identified as an irritant by the ATSDR and the EPA.

22 Would you like to include that on the list?

1 Any concerns?

2 DR. BURNS: I mean, it's specifically
3 mentioned as a lung irritant.

4 DR. HATSUKAMI: Right.

5 DR. BURNS: Which would suggest that,
6 certainly, at this point, it should be included.

7 DR. HATSUKAMI: Yes.

8 Any objections?

9 [No response.]

10 DR. HATSUKAMI: Okay. So we'll go ahead and
11 include that.

12 Now, we come to acrolein, which has been
13 identified by HSDB, as well as Dr. Wynder, as a
14 respiratory irritant.

15 DR. BURNS: And when Erik Dybing and his
16 colleagues did a non-cancer respiratory response index
17 for the WHO report, that was the one that came out an
18 order of magnitude higher than anything else.

19 DR. HATSUKAMI: Okay. So we include that on
20 the list.

21 Any concerns? Yes, Dr. Lauterbach?

22 DR. LAUTERBACH: Just one thing here.

1 Things like acetone, acrolein, whatever, are known to
2 be in mainstream cigarette smoke. They're routinely
3 measured. And I'm wondering, in terms of the
4 carbonyls, whatever, do we need just to go into these
5 in detail, but just basically include them in because
6 they're typically measured.

7 DR. HATSUKAMI: Any comments?

8 DR. BURNS: Well, the purpose of this
9 review, as I understand it, is to certify that what is
10 being included on the list is something that, indeed,
11 has toxicity rather than simply that it's routinely
12 measured. So I think we do need some certification by
13 this group that there is a toxicologic reason for
14 being on the list.

15 DR. HATSUKAMI: That's my understanding,
16 that we're identifying harmful and potentially harmful
17 constituents.

18 Okay. Let's go on.

19 Ammonia, and that has been identified by the
20 ATSDR, as well as on the Hoffmann & Hoffmann list, and
21 it's a respiratory irritant.

22 Any objections?

1 [No response.]

2 DR. HATSUKAMI: Okay.

3 The next one is butyraldehyde, and that has
4 been identified as a -- it's a smoke-related -- it's
5 associated with chronic obstructive lung disease.
6 It's on a Hoffmann -- it was signed by Hoffmann. It
7 also is associated with increased blood pressure in
8 animal studies, and it is said to play a role in lipid
9 peroxidation. Studies are cited for that.

10 Any concern about adding that onto the list?

11 No?

12 Dr. Farone?

13 DR. FARONE: Not a concern, just an
14 observation. Many of these have more than one
15 indication.

16 DR. HATSUKAMI: Yes.

17 DR. FARONE: And we mentioned, also,
18 reproductive harm. I presume that on our list we'll
19 have more than one category going across. So that if,
20 for example, it was decided later that it wasn't a
21 carcinogen, FDA would be reminded, well, yes, but it
22 still is either a cardiovascular risk or respiratory

1 risk.

2 In other words, I'm really suggesting that
3 the list be not one-dimensional, but that across from
4 all the chemicals, we list the dimensions of the toxic
5 -- the reason that it's on the list.

6 DR. HATSUKAMI: Whether it's related to
7 cardiovascular or respiratory is what you're saying,
8 or both.

9 DR. FARONE: Whatever we know about it.
10 Whatever we know about it, yes.

11 DR. HATSUKAMI: Okay. Or cancer.

12 DR. HENNINGFIELD: And similarly, we've
13 already mentioned a couple that are on the addiction
14 list, but right now, just to be clear, we're not
15 covering that.

16 DR. HATSUKAMI: Right, not right now.
17 Yes?

18 DR. BURNS: Dorothy, let me raise a process
19 concern. If we're going to do that, then we need to
20 review them all for that purpose. That is, the ones
21 that are already carcinogens will have to be re-
22 reviewed in order to assess whether they have

1 respiratory, cardiovascular, addiction and other
2 potential toxicities.

3 I'm also a little bit uncomfortable in
4 trying to expand from the concept that something has
5 an irritant capacity in the lung or an irritant
6 capacity, per se, to stating that it has respiratory
7 and/or cardiovascular toxicity relative to COPD and
8 heart disease.

9 I'm sensitive to the fact that we don't have
10 good metrics by which we can go from animal testing,
11 for example, through to human COPD and human vascular
12 disease, and that some of the citations for vascular
13 disease are intermediate steps in the methodology that
14 haven't been validated as predicting subsequent
15 events.

16 So I think we need to be a bit cautious
17 about saying that we can define, for each of these
18 events, each specific toxicity. And I think perhaps
19 Bill's concern can be addressed by putting in a
20 statement that this is what we did.

21 Multiple toxicities have been identified for
22 many of these agents. If an agent is being considered

1 for being dropped from the list, all of the separate
2 toxicities should be considered independently before
3 the decision is made to drop it.

4 DR. HATSUKAMI: Any objections to that
5 comment?

6 Dr. Lauterbach? I'm sorry.

7 Dr. Farone? I'm sorry.

8 DR. FARONE: In principle, I agree with
9 Dr. Burns. Where it says, however -- like, if you
10 look at cadmium, because we were at carbon monoxide,
11 where the ATSDR, which is one of the criteria that
12 we've talked about accepting, has found it to be
13 respiratory and says that there is some evidence that
14 cadmium may accelerate the development of emphysema in
15 smokers, it would seem that then it meets the criteria
16 both ways. And if we have the information -- I'm not
17 suggesting that we go back and review everything for
18 everything. I'm just suggesting that where the
19 information is readily available, we could simply put
20 it on the list so that the FDA would be reminded, when
21 they read that thing about cadmium, it's not just
22 cancer.

1 DR. BURNS: Yes. And certainly, in cadmium,
2 that's one example where the process has been
3 completed through to human evidence of disease from
4 that exposure in an occupational setting. So there,
5 the change is complete.

6 DR. HATSUKAMI: I think for our
7 deliberations today, I think one of the things that we
8 should do is just identify what should be on the list
9 and off the list. And maybe for the subsequent
10 meeting in July, we could be a little bit more
11 specific.

12 Is that okay?

13 So let's take a look at butyraldehyde. This
14 is a constituent that has been identified through
15 literature review.

16 Do people feel that that's sufficient to
17 include that on the list? Okay. No objections?

18 [No response.]

19 DR. HATSUKAMI: Okay.

20 Carbon monoxide? That's associated with
21 cardiac symptomatology or ischemic episodes.

22 DR. BURNS: There also has been a fair

1 amount of evidence off and on again about whether
2 carbon monoxide does or doesn't increase the
3 underlying risk of atherosclerotic disease on a
4 mechanistic basis. I don't believe that that's
5 currently conclusive at this point in time, but it
6 certainly has independent defined toxicity,
7 independent of cardiovascular disease.

8 Obviously, there are toxicities that have
9 been identified in people who are cigarette smokers
10 that relate to increased hemoglobin and increased
11 responses in terms of hematocrit, as well. And so
12 there is reason to put it up because of its direct
13 acute toxicities, as well as its chronic toxicity.

14 DR. HATSUKAMI: Okay. It sounds like it's
15 to be included. All right.

16 Eugenol? That's been identified by the
17 HSDB, as well as in the literature, to be a
18 respiratory irritant. Any concerns about adding that
19 onto the list?

20 [No response.]

21 DR. HATSUKAMI: No? All right.

22 The next one is glycerol. So glycerol --

1 carbon monoxide, acetaldehyde and acrolein can be
2 formed when glycerol is decomposed by heat. So it
3 doesn't sound like it's a direct toxicant, but it can
4 convert to constituents that may be and that are
5 toxic.

6 DR. BURNS: On the list we were given, it's
7 listed as a content rather than as a smoke
8 constituent, and I'm not sure it appears in smoke very
9 much in a unmodified form.

10 DR. HATSUKAMI: Dr. Lauterbach?

11 DR. LAUTERBACH: Okay. Number one, glycerol
12 does transfer into smoke fairly readily. It's out
13 there in the literature. It's easy to find. I do
14 caution the committee's use of pyrolysis data and
15 small molecules, where it was not done in tobacco, it
16 was done in pyrolysis equipment.

17 There have been numerous cases in the
18 literature where pyrolysis of relatively small
19 molecules does not give the same thing as pyrolysis
20 within the cigarette.

21 DR. HATSUKAMI: Dr. Heck, and then Dr.
22 Farone.

1 Dr. Heck?

2 DR. HECK: Yes. Reinforcing what John has
3 mentioned, there is a considerable literature on the
4 fate of glycerol in burning cigarettes. It is used as
5 a humectant ingredient. So there's several there
6 looking at the evolution of acrolein, which is usually
7 the issue raised, and the transfer into smoke. And
8 the committee is welcome to review those studies. I
9 can help you get them.

10 But long story short, the evolution of
11 acrolein from glycerol in cigarettes is minimum. It's
12 not significant. Glycerol is transferred largely
13 intact into the smoke stream.

14 DR. HATSUKAMI: Dr. Farone?

15 DR. FARONE: Just a process question,
16 observation, I guess. On many of these lists, it was
17 noted yesterday, you have a compound that's looked at
18 in tobacco and then we have the smoke constituents.
19 And it is a smoke constituent, but if you look at it
20 in isolation, it's probably one of the most -- I won't
21 use the word harmless, but it's one of those
22 constituents for which, in and of itself, there's very

1 little evidence.

2 In other words, you have to look at what
3 happens on combustion and pyrolysis, which would then
4 -- I mean, just a little bit. I think what we're
5 talking about right now are things that are in the
6 smoke and not things which we put in the cigarette,
7 which then may become something that you worry about
8 in smoke.

9 So I don't know that I would include it on
10 the list of smoke constituents as something of hazard
11 value. If we had a different list for ingredients
12 that might create toxicants when oxidized or
13 pyrolyzed, then I think it would definitely be on the
14 list. So it's just a question of process, I guess.

15 DR. HATSUKAMI: Dr. Watson?

16 DR. WATSON: I agree with what's been said.
17 My understanding is glycerol is used at fairly high
18 levels. And so that it could impact measurement of
19 something like, for instance, tar, particularly in
20 something like the club cigarette, where the tar
21 fraction might have a significant portion of glycerol
22 in there.

1 For that reason, it might be important to
2 measure, even though it's not particularly toxic
3 itself or there's no toxic properties associated with
4 it directly. But if one wanted to use, say, for
5 instance, tar to normalize other things, as has been
6 mentioned earlier in the meeting, that might be an
7 important thing to know.

8 If the tar fraction is substantially -- if
9 it contains a substantial amount of glycerol, that
10 would be an important thing to know when making
11 product comparisons. So it could impact the analysis
12 of other compounds. So, therefore, I would suggest it
13 be included, even though it may not be terribly toxic
14 itself.

15 DR. HATSUKAMI: Dr. Heck?

16 DR. HECK: I think a lot of this discussion
17 will apply to propylene glycol, when we come to that.
18 Both glycerol, glycerin and propylene glycol are used
19 as humectant ingredients in the products, and since,
20 certainly, the product ingredients are well within the
21 purview of this regulatory scheme we're entering,
22 certainly, the toxicity or lack thereof of the

1 ingredients will be thoroughly examined.

2 I think I agree with what I thought I heard
3 Dr. Farone saying, that maybe the purposes of this
4 committee would be best served if we focused, to the
5 extent we can, on the endogenous, intrinsic tobacco
6 and smoke constituents and set aside, maybe, for this
7 purpose, the effects of the intentionally added
8 ingredients, which will be covered elsewhere.

9 DR. HATSUKAMI: Any other comments?

10 Dr. Burns?

11 DR. BURNS: I think on a process level, we
12 need to be very careful, because if we're going to
13 examine or put things on the list because of their
14 impact on other smoke constituents that were already
15 measured, particularly ones we're already measuring,
16 then that's going to cover lots of other compounds
17 that are added to or are present in smoke.

18 I understand vividly the issue of being able
19 to control for the mass of smoke and do it
20 appropriately, but I think our task is to define
21 toxicants in smoke rather than the process by which we
22 would assess how those toxicants should be regulated

1 or counted.

2 Certainly, there would, I would expect, be
3 an additional step as you move from a list of
4 toxicants to how you're going to implement that list
5 for purposes of measuring and monitoring changes in
6 tobacco over time. And at that step, I think issues of
7 adding other substances that add mass in order to
8 drive the tar value up, to reduce the level of
9 constituent per milligram of tar, for example, would
10 be a very valid point to consider measuring glycerol.

11 But if our task here is to measure toxicity,
12 I think we need to be bound by the toxicity of the
13 actual substance present in the smoke or absorbed by
14 the individual.

15 DR. HATSUKAMI: Any other comments?

16 Dr. Heck, and then Dr. Farone.

17 DR. HECK: Just one more follow-up to my
18 suggestion earlier. Glycerol, for instance, and
19 propylene glycol and the other actual ingredients that
20 are up here on this tentative list, there is a vast
21 published literature on the toxicity or lack thereof
22 of these ingredients -- animal studies, human lung

1 deposition, retention studies, a lot of things -- and
2 it's not really reflected in this data summary here.
3 So another maybe rationale for considering those
4 fully, but not necessarily in this context.

5 DR. HATSUKAMI: Dr. Farone?

6 DR. FARONE: I'm in favor of the footnote
7 kind of approach to some of these, especially where
8 they might be relevant to problems in tobacco as
9 opposed to smoke. And let's not forget chewing
10 tobacco and other things where, also, it can dilute or
11 it might have some other attributes.

12 So I think Cliff's comment was very well
13 taken. And is that not possible, something that we
14 can handle for some of these as a footnote to the list
15 that we're preparing, that there might be some other
16 relevant reasons for looking at some compounds, for
17 example, to clarify the situation with regard to tar?

18 That's true of propylene glycol, too. You
19 do get a lot of transfer of it and you can certainly
20 reduce -- you can make it look, the smoke, better by
21 using a lot of glycerin in the products.

22 DR. BURNS: Well, it goes to, I think, the

1 title of the list. If the title of the list is things
2 that should be measured in tobacco, then I have no
3 difficulty with that.

4 If the title of the list is toxicants
5 present in tobacco smoke, which is what I thought the
6 task was here, then I think that can be included in
7 the text as other things that would be appropriate to
8 measure in tobacco in order to understand how these
9 toxicants should be examined. But I'm concerned about
10 putting something on as a toxicant when there isn't
11 data to support it.

12 DR. HATSUKAMI: Dr. O'Connor?

13 DR. O'CONNOR: I'll let Dr. Husten --

14 DR. HATSUKAMI: Dr. Husten?

15 DR. HUSTEN: I just wanted to remind the
16 committee of one of the parameters from yesterday,
17 which is to focus on harmful and potentially harmful
18 constituents that are potentially ingested, absorbed
19 or inhaled; that is, absorbed from the product itself
20 or combustion products that are inhaled.

21 DR. HATSUKAMI: Dr. Burns?

22 DR. BURNS: That's the issue that I'm

1 raising.

2 DR. HATSUKAMI: So what I'm hearing is that
3 we should probably take glycerol off the list and
4 potentially have a footnote as something to look at
5 that.

6 Okay. Great. So off the list. All right.

7 Hydrogen cyanide. That's been identified as
8 a potential respiratory toxicant by the ATSDR and
9 potentially a cardiovascular-related toxicant by the
10 ATSDR, as well.

11 Any objection to including that?

12 [No response.]

13 DR. HATSUKAMI: No? Okay.

14 Methyl ethyl ketone. That has been
15 identified as a respiratory irritant by the ATSDR.

16 Any objections to including that?

17 Did I skip something?

18 I'm sorry. What did you say?

19 DR. LAUTERBACH: On my sheet, after HCN, I
20 have hydroquinone. I thought I heard methyl ethyl
21 ketone.

22 DR. HATSUKAMI: Yes. It's already on the

1 list.

2 So just to go back, the methyl ethyl ketone,
3 any objections to that being on the list?

4 [No response.]

5 DR. HATSUKAMI: Okay.

6 Nicotine?

7 DR. BURNS: What do you think, Jack?

8 DR. HENNINGFIELD: Well, actually, it's
9 surprising that we don't have it listed for other than
10 addictive, because at high doses, it has a variety of
11 other toxicological effects.

12 DR. BURNS: Certainly, reproductive.

13 DR. HATSUKAMI: Reproductive, yes. I think
14 we should include it on the list. It's addictive,
15 reproductive.

16 I'm sorry. Dr. Farone?

17 DR. FARONE: We skipped myosmine.

18 Are we not going to put that on?

19 DR. HATSUKAMI: I think the myosmine is for
20 the addiction, right?

21 DR. FARONE: Yes. But is it only?

22 DR. HATSUKAMI: I think the thought --

1 Corinne? I'm sorry.

2 DR. HUSTEN: So just to clarify two things.
3 One, if the substance was on the carcinogen list and
4 there wasn't anything in the initial literature review
5 that suggested respiratory or cardiovascular, it was
6 just on the carcinogen list, things that had some
7 evidence of respiratory or cardiovascular were placed
8 on this list.

9 But then if they were also a carcinogen,
10 they're labeled as such, because yesterday the group
11 had said if it's a carcinogen, we don't need to
12 necessarily go through everything.

13 I thought I heard yesterday around the minor
14 alkaloids that we needed a NIDA presentation. So for
15 the time being, they're on a footnote to be discussed
16 at the next meeting.

17 DR. HATSUKAMI: Yes. So the addictive ones
18 are going to be discussed next time.

19 All right. Nitrate. That is considered to
20 be a respiratory -- related to respiratory function,
21 and that was identified by Hoffmann & Hoffmann in
22 1997.

1 Any concerns about putting that on the list?

2 Yes, Dr. Heck?

3 DR. HECK: I don't know if it's a concern.

4 Just a comment. The suggestions here that nitrate is
5 a precursor for other entities, it may be a greater
6 concern. I think we have captured all of those
7 downstream purported products of nitrate, if that's a
8 factor in our consideration here, elsewhere on the
9 list.

10 DR. HATSUKAMI: Dr. Farone?

11 DR. FARONE: Well, nitrate is kind of
12 special because of the ease with which it helps make
13 in the smoke the nitrosamine. So I think if it's
14 present in smoke as something in and of itself and it
15 is a respiratory irritant, although it's not -- I
16 mean, this is just in the Hoffmann & Hoffmann list --
17 it may be something we want to keep, because
18 chemically, in terms of its activity in smoke, if you
19 just take a little bit of it and mix it with nicotine,
20 you can make NNK without too much trouble.

21 DR. HATSUKAMI: Any comments?

22 Dr. Burns?

1 DR. BURNS: Again, the issue comes up as to
2 whether we are putting it on the list for its own
3 intrinsic toxicity or whether we're putting it on the
4 list because it facilitates the development of other
5 things that are toxicants, particularly if we're
6 already measuring those other toxicants, such as the
7 nitrosamines and ammonia.

8 Again, I have a concern that if we're going
9 to do that for individual compounds that are present
10 in the contents of tobacco, then we need to have a
11 more expansive review of those substances, because
12 there's a lot of them that we would be concerned about
13 as additives to tobacco, how they modify the
14 subsequent toxicity of the smoke.

15 DR. FARONE: No. I agree with that 100
16 percent. I'm just saying that if we feel that, in
17 smoke, this is in smoke, whether you find nitrate in
18 the particles of some itself or whether they've
19 already -- if they've already reacted, then, I agree,
20 there's no point in looking for something that isn't
21 there.

22 If smoke has a content of nitrate, which is

1 in the smoke, and as that smoke is used, it's going to
2 cause a reaction, say, in the lung or in the mouth or
3 other places, and if it, in and of itself, as this
4 says, is a respiratory effect, then that would be the
5 reason for including it; otherwise, not.

6 So I think we're really in agreement on
7 this.

8 DR. BURNS: Except that it does not say
9 that, at least as far as I can interpret it. It says
10 that some of the nitrate in tobacco is reduced during
11 smoking to NH_2 minus amine and ammonia -- I'm just
12 reading what's there -- which suggests that it's not
13 the nitrate, per se, that causes the respiratory
14 irritation, but rather the consequences of its
15 presence in the tobacco.

16 I'm willing to defer to people who actually
17 have more knowledge of chemistry than my high school
18 provided me.

19 DR. HATSUKAMI: Okay. Dr. Farone, and then,
20 Dr. Hecht, if you want to make a comment.

21 Dr. Farone?

22 DR. FARONE: Well, that was the question I

1 was really asking. Is there enough evidence to
2 include it as a respiratory problem? I'm open on this
3 either way. I don't see the evidence that, in and of
4 itself, in smoke, it causes a respiratory problem, but
5 I don't know the answer to that.

6 DR. HATSUKAMI: Dr. Hecht?

7 DR. HECHT: Dorothy, I'm a little confused.
8 Are we doing just smoke now or smoke and tobacco?

9 DR. HATSUKAMI: It's smoke and tobacco.

10 DR. HECHT: So why are we talking about
11 smoke?

12 DR. HATSUKAMI: Well, no, we include
13 tobacco, as well.

14 DR. HECHT: So this list is everything.

15 DR. HATSUKAMI: Yes.

16 DR. HECHT: It could be in smoke or it could
17 be in tobacco.

18 DR. HATSUKAMI: It could be in tobacco.

19 DR. BURNS: Then we need to have a much more
20 expansive list then. I mean, it's not clear to me.
21 This is a list that was derived from what's in smoke.
22 That's the origin for much of what's on the list.

1 There are a few things that have been
2 measured as contents, and we have been removing
3 things, like glycerol, that are important content
4 metrics in terms of knowing what's going on with the
5 tobacco, because they don't have toxicity in the
6 smoke.

7 I understood, from what we were asked to do,
8 that we were talking about things that are inhaled.
9 If that's not true --

10 DR. HATSUKAMI: No.

11 DR. BURNS: -- then we need to expand it to
12 a broader list of considerations, I think. There's
13 all the sugars and a whole bunch of other things that
14 come up as to whether they make a meaningful
15 contribution. So I'm just confused, I guess, as to
16 what we're doing.

17 DR. HATSUKAMI: Dr. Husten?

18 DR. HUSTEN: The charge is tobacco products,
19 but it's also what is harmful or potentially harmful
20 that's ingested, absorbed or inhaled.

21 DR. HATSUKAMI: So it is everything.

22 Dr. O'Connor?

1 DR. O'CONNOR: So maybe as a process thing,
2 we go through smoke, then we go back and we go through
3 whole tobacco.

4 DR. HATSUKAMI: Yes. I think that that's
5 what we should do.

6 Dr. Farone?

7 DR. FARONE: Well, certainly, ingestion is
8 bad for nitrate. So if we're talking about nitrate in
9 tobacco and we're talking about oral tobacco use, then
10 it stays on the list. So just a question, again, of
11 the purpose of the list.

12 If it's all inclusive, I think then this
13 list doesn't tell you all of the potential toxicology
14 ramifications, because ingestion has to be added as to
15 what can be ingested.

16 DR. HATSUKAMI: Right.

17 Dr. Henningfield?

18 DR. HENNINGFIELD: He just made my point.

19 DR. HATSUKAMI: Dr. Lauterbach?

20 DR. LAUTERBACH: Just one comment about the
21 nitrate in tobacco and oral tobacco products. There's
22 nitrate in plenty of other food, vegetables, whatever,

1 and I'd like to know where nitrate in smokeless
2 tobacco products is a toxicological problem.

3 DR. HATSUKAMI: Dr. Farone, and then Dr.
4 Henningfield.

5 DR. FARONE: If you mix it with a little bit
6 of any of the alkaloids in saliva and look for the
7 formation of nitrosamines, you'll find it.

8 DR. HATSUKAMI: Dr. Henningfield?

9 DR. LAUTERBACH: Do you have a literature
10 reference on that I can check?

11 DR. FARONE: I think, Steve. I don't
12 remember exactly the conditions under which that
13 occurs, but --

14 DR. HECHT: It's nitrite you're thinking of,
15 not nitrate. Nitrite.

16 DR. FARONE: Yes. As it's reduced, though.

17 DR. HECHT: Right.

18 DR. HATSUKAMI: Dr. Henningfield?

19 DR. HENNINGFIELD: My comment has been
20 covered again. Dr. Farone is one step ahead of me.

21 DR. HECHT: Dorothy?

22 DR. HATSUKAMI: Yes. Dr. Hecht, then

1 Dr. Burns.

2 DR. HECHT: I think we need to make separate
3 lists for smoke and tobacco. So why don't we -- I
4 mean, it's up to you. But shouldn't we go through
5 this and -- we've been thinking smoke all along. So
6 we should go through this and make a list for smoke
7 and then go back and make a list for tobacco.

8 DR. HATSUKAMI: Yes. That's what
9 Dr. O'Connor had mentioned. So I agree with that. So
10 now what we're doing is we're focusing on smoke. Then
11 we'll go back and focus on tobacco.

12 So should nitrate be part of the smoke?

13 Yes, Dr. Farone?

14 DR. FARONE: Dr. Hecht's comment is
15 perfectly correct. It's the reduction of nitrate to
16 nitrite that occurs that then reacts. But still, the
17 principle is if you start with nitrate, you can form
18 it.

19 Then the question is in the oral products,
20 when we get to it, is that something we want to put on
21 the list. I still think it is.

22 DR. HATSUKAMI: Let's go through this as

1 smoke emissions, and then we'll talk about it as an
2 oral tobacco or tobacco constituent.

3 So nitrate should be off the list is what
4 I'm hearing. Right? Okay. All right.

5 As a smoke constituent. Yes?

6 DR. HUSTEN: I feel like maybe there's still
7 a little bit of confusion. So just in the interest of
8 clarifying this, I've been reading the parameters, but
9 I feel like maybe that's not quite as clear as it
10 appeared to be when I was writing those parameters.

11 So what we're asking the committee to focus
12 on, constituents that are harmful or potentially
13 harmful as it's absorbed in people. So we defined a
14 constituent as what gets into people, basically.

15 So we're asking the committee to focus on
16 harmful and potentially harmful constituents that
17 people are exposed to as opposed to necessarily where
18 that route comes from. It's like what is the list of
19 constituents that, as people are exposed to them, are
20 harmful, whether it's from a smokeless tobacco product
21 or from smoke.

22 DR. HECHT: But that list will be different

1 for smoke and tobacco.

2 DR. HUSTEN: Right. But I just wanted to be
3 clear that it's what people are exposed to, not
4 necessarily where it comes from, that's the focus of
5 the committee.

6 DR. HATSUKAMI: Right. And I think we know
7 that, and I think it's just a matter of just being a
8 little more focused on the smoke right now, and the
9 list may be somewhat similar to other tobacco
10 constituents.

11 Yes, Dr. Burns?

12 DR. BURNS: And for purposes of any
13 meaningful use of this list, you certainly are not
14 going to measure in tobacco all of the combustion
15 products that we have identified here.

16 So if you're going to use this list, it has
17 to be separated into things that you would feel
18 obligated to measure in smoke, and you wouldn't,
19 obviously, measure all of those in tobacco, as well.

20 DR. HATSUKAMI: Yes?

21 DR. FARONE: Just to emphasize that, I mean,
22 we had this discussion about nitrate and it might be

1 if you just take nitrate alone and you just ingest it,
2 that's not a good thing. So it's, what, 10 parts per
3 million in water before it's considered to be a
4 problem.

5 But I think what we're doing, process-wise,
6 just to make sure, we're going to have this list and
7 then we'll go back and look at the tobacco category as
8 being something extra.

9 DR. HATSUKAMI: Right. Okay. All right.
10 The next is the nitric oxide/nitrogen oxides. It's
11 identified as a lung inflammation -- cause of lung
12 inflammation, according to the Hoffmann list, and it's
13 a likely chemical to cause ischemic heart disease,
14 according to Dr. Benowitz, Neal Benowitz.

15 On the list? Any concerns?

16 [No response.]

17 DR. HATSUKAMI: Okay.

18 Next is phenol. Phenol is considered to be
19 toxic to ciliated cells in the lung, according to
20 Wynder, and it is considered to be a potential cause
21 for cardiac dysrhythmias, according to ATSDR.

22 On the list? Okay.

1 DR. BURNS: It certainly is a ciliotoxic and
2 I know that there's been some concern expressed about
3 its credentials as a carcinogen. But it certainly is
4 ciliotoxic.

5 DR. HATSUKAMI: Okay. Propionaldehyde is
6 toxic to the ciliated cells, according to Wynder, and,
7 also, related to -- considered to contribute to
8 smoking-related chronic obstructive lung disease,
9 according to Hoffmann. It also is considered to be
10 associated with sympathomimetic effects, which would
11 lead to increased risk for cardiovascular disease, and
12 that's identified according to a couple of references.

13 So what is the feeling about the committee
14 regarding including that on the list? Any objections?

15 [No response.]

16 DR. HATSUKAMI: Okay. That will be
17 included.

18 Propylene glycol, I guess, we had some
19 discussions on before. My thought is that we should
20 exclude that from the list.

21 Is that right? Okay.

22 Do we want to have a footnote on propylene

1 glycol, similar to what we decided on the glycerol?

2 Yes. Okay.

3 Pyridine. In rats, it exhibited adverse
4 respiratory effects, described as inhibited lipid
5 formation and decreased protein synthesis and
6 phospholipid content. That was identified as a
7 respiratory tract irritation according to the Hoffmann
8 list.

9 Any objection in terms of including
10 pyridine?

11 [No response.]

12 DR. HATSUKAMI: No? Okay.

13 DR. BURNS: Just as a matter of form, we
14 should also probably include the notation, where it's
15 appropriate, that other national entities have
16 identified it as something that should be on the list
17 of toxicants measured in smoke. In this case, I think
18 both Canada and Brazil have identified it.

19 In using the approach that we're using of
20 incorporating, I think it's useful to provide that
21 notation, as well.

22 DR. HATSUKAMI: Okay. Good point.

1 Resorcinol. It's considered to be a
2 respiratory irritant, according to HSBDB, and, also, a
3 toxicant to ciliated cells.

4 Any concerns about including that on the
5 list?

6 [No response.]

7 DR. HATSUKAMI: No? Okay. All right.

8 Selenium. It's considered to be a lung
9 toxicant, respiratory toxicant, according to ATSDR.
10 Any concern about including that? Yes?

11 DR. HECK: Not a particular concern about
12 this metalloid. It doesn't differ from the same
13 concern with a lot of these. A lot of these effects
14 that are listed in ATSDR, for instance, these are all,
15 of course, dose-response phenomenon and, at some
16 point, we will have to or the full committee will have
17 to take a second pass through these and really try to
18 make a judgment as to whether the quantities present
19 in smoke or smokeless tobacco really are sufficient to
20 invoke these kinds of concerns.

21 Just a comment, because we have essential
22 nutrients and natural body constituents on this list

1 and the importance of food and our everyday
2 environment. Certainly, at some level or in some
3 instances, large quantities in a warehouse fire can
4 produce toxic pyrolysis products, but at levels of
5 sorbic acid and things like that that would be present
6 in products.

7 We really shouldn't be concerned about the
8 contribution of carbon monoxide, for instance. It's
9 already prominent in smoke.

10 DR. HATSUKAMI: Okay. That's noted. So it
11 appears that selenium should be included.

12 DR. DJORDJEVIC: Well, I just wanted to say
13 that selenium is one of the food supplements and it is
14 often recommended as a chemopreventive agent; so kind
15 of these two informations don't go hand-in-hand.

16 DR. BURNS: One of the issues that we need
17 to be concerned with, I think, is that many of these
18 compounds have been identified as causing substantive
19 lung injury in high dose exposure over modest periods
20 of time, either acute or occupational exposures.

21 You have the concern about the contribution
22 that they then would make in the context of all of the

1 other constituents of smoke to the development of
2 further lung injury.

3 So I would urge, as we commonly do for
4 environmental and occupational exposures to err on the
5 conservative side. If you have a clear, demonstrated
6 potential for an agent to cause lung injury, then we
7 need to be cautious that we don't dismiss it based on
8 what would happen if only that level of only that
9 agent was inhaled for a period of time.

10 I'm not suggesting that we have certainty
11 there one way or the other, but I do feel that the
12 normal process by which we would think about these
13 things would lead us to be very cautious about
14 excluding the possibility that these agents can make a
15 contribution when they are demonstrated to be toxic in
16 higher doses.

17 DR. HATSUKAMI: So, Dr. Burns, it seems like
18 you're saying that we should include selenium, because
19 in higher doses, it might be --

20 DR. BURNS: Right. And it's recommended for
21 chemoprevention. It's not as an inhalation,
22 certainly.

1 DR. HATSUKAMI: Okay.

2 Did someone have their hand up?

3 Dr. Lauterbach?

4 DR. LAUTERBACH: Just one point. Adding to
5 the literature on selenium, there was a study done by
6 U.S. Government scientists, where they added selenium
7 to the tobacco and wound up with reduced AIMS activity
8 of the condensate, smoke condensate.

9 DR. HATSUKAMI: Dr. Farone?

10 DR. FARONE: If I recall correctly, Dr.
11 Jinot can correct me, this is a TCLP metal, selenium.
12 Yes. It's on the EPA list of primary things to worry
13 about being extracted into the aquifer. So that would
14 be an ingestion thing, not necessarily inhalation.
15 But I think my recommendation is we keep it on until
16 we have a little bit clearer picture of what it might
17 or might not do.

18 DR. HATSUKAMI: Okay. So we're going to
19 keep it on, unless there's any other comments. Okay.

20 The next one is sodium propionate. And that
21 is another one where, as a combustion product, it
22 creates carbon monoxide. So that's very similar to

1 some of our other concerns.

2 Dr. Farone?

3 DR. LAUTERBACH: Let Dr. Farone go first.

4 DR. FARONE: Okay. I think the next two,
5 sodium propionate and sorbic acid fall into --
6 especially the sorbic acid falls in the same category
7 as the glycerin. It's something that, if it does
8 transfer, just dilutes the tar really.

9 DR. HATSUKAMI: All right. So is this a
10 footnote one? Not to include for smoke.

11 Dr. Lauterbach?

12 DR. LAUTERBACH: Sodium propionate is used
13 as a preservative both in some manufactured tobaccos
14 for cigarettes, or has been. It's used as a
15 preservative in smokeless tobacco products, in some
16 cases. The same with sorbic acid.

17 But I don't think any of the information you
18 have on here relates to any sort of meaningful
19 pyrolysis as far as smoke toxicants are concerned.

20 DR. HATSUKAMI: So you're suggesting no
21 footnote. Okay.

22 DR. HECK: And I think there is an analogy,

1 as Dr. Farone mentioned, with the glycerol situation.
2 However, these preservatives, the levels of use are,
3 if not orders of magnitude, far, far lower than the
4 humectants.

5 DR. HATSUKAMI: So exclude from list,
6 exclude as footnotes is what I'm hearing. Okay.
7 Great. Good. Sorbic acid, as well.

8 Toluene. That's considered a respiratory
9 tract irritant by the ATSDR.

10 Include on the list? Any objections?

11 [No response.]

12 DR. HATSUKAMI: Okay. That's included on
13 the list.

14 Triacetin. So this is another hazardous
15 combustion product. It leads to a hazardous
16 combustion product, carbon monoxide.

17 DR. LAUTERBACH: Clarification, please, on
18 that.

19 DR. HATSUKAMI: I'm sorry. On toluene?

20 DR. LAUTERBACH: There's no evidence that
21 triacetin, which is mainly used as an additive in
22 cigarette filters, sometimes uses a carrier for

1 flavors, there's no evidence out there that that's
2 hazardous combustion products.

3 It transfers readily into smoke and it's
4 commonly used in most filtered American cigarettes and
5 filter cigarettes around the world. And I don't think
6 anything has come back where that's being a hazardous
7 combustion product, either used as a filter additive
8 or used as part of a flavor carrier.

9 DR. HATSUKAMI: I think it says it leads to
10 a hazardous combustion product that can include carbon
11 monoxide. But it sounds like, based upon our other --
12 the way that we've dealt with the other constituents,
13 that we should actually not include that on the list.

14 DR. HECK: I would concur, Madam Chairman.

15 DR. HATSUKAMI: All right. Do not include.

16 Triethylene glycol. That's another one
17 where the combustion of triethylene glycol includes
18 some potentially harmful constituents. So that's
19 another instance, again, where this ingredient itself
20 may not necessarily be hazardous.

21 Yes, Dr. Farone?

22 DR. FARONE: Yes. That's the same as the

1 glycerin and the propylene glycol.

2 DR. HATSUKAMI: Okay. Should we have a
3 footnote on this one?

4 DR. FARONE: I think so, yes.

5 DR. HATSUKAMI: Okay. All right. Do not
6 include, and it should have a footnote.

7 All right. I think we're done with the
8 list. So what we've done is we've identified the smoke
9 constituents.

10 Do we need a break? Why don't we take a 15-
11 minute break, and then what we will do is we'll go
12 through this list again and identify constituents in
13 tobacco that may be harmful or potentially harmful.

14 Yes, Dr. Burns?

15 DR. BURNS: We probably need some discussion
16 about -- before we go through a list, some discussion
17 about why we're including things that are in tobacco
18 and what criteria we're going to be using.

19 The lists that are out there are not
20 including things because they're toxicants in tobacco.
21 They're often including things because they describe
22 how the manufacturing process is being changed with

1 different products.

2 The Canadians, for example, are measuring
3 content issues for that reason. And if we are going
4 to identify primary toxicants, then we need to have
5 some discussion of the criteria we're going to be
6 using to identify the toxicants that are present in
7 the tobacco and, for that matter, the documentation
8 that they are, indeed, present.

9 DR. HATSUKAMI: Right. I would agree with
10 that. So similar to what we had done with smoke
11 emissions. Okay.

12 Why don't we take a 15-minute break? And I
13 guess I need to read something before we break.

14 We will now take a short 15-minute break.
15 Committee member and consultants, please remember that
16 there should be no discussion of the meeting topic
17 during the break amongst yourselves or any member of
18 the audience.

19 So we will return in 15 minutes.

20 (Whereupon, a recess was taken.)

21 DR. HATSUKAMI: Okay. I think we'll go
22 ahead and get started.

1 Our next charge is to identify harmful or
2 potentially harmful constituents in smokeless tobacco
3 products, and we're thinking about constituents that
4 are harmful or potentially harmful when ingested.

5 So just for the subcommittee members and
6 consultants, to be clear, it's not tobacco, per se,
7 but smokeless tobacco products and harmful and
8 potentially harmful when ingested.

9 What we're going to do is we're going to go
10 through the list, the summary list that was provided
11 to the committee members and consultants as background
12 material. And what we'll do is we'll identify the
13 constituents that were identified as being -- we're
14 going to look at the constituents that were identified
15 as being potentially harmful or harmful by different
16 countries and by different criteria.

17 So if we can look at that.

18 Yes, Dr. Burns?

19 DR. BURNS: Before we get halfway through
20 this and have to redo it, what criteria are we using
21 for that definition? Specifically, we have talked
22 about several compounds that, when they are altered in

1 form, produce things that are toxic, such as burning
2 glycerol, et cetera.

3 Is that criteria for inclusion or are we
4 talking about the glycerol present in tobacco ingested
5 as glycerol? That's one question.

6 The second question that I have great
7 anxiety about is if we're talking about things that
8 might modify other characteristics of the product,
9 specifically, ingestion of nicotine, with things that
10 might or might not alter the pH of the smoke, et
11 cetera, are we going to include those? Because nobody
12 has gone back and done an analysis of tobacco to
13 identify all of those, as a governmental entity, at
14 least that I'm aware of.

15 So I think we need some kind of decision on
16 the front end about what we're doing before we get too
17 far into this process.

18 DR. HATSUKAMI: My understanding is, for
19 example, if glycerol was as ingested, if that was
20 considered to be harmful or potentially harmful, then
21 we include that on the list.

22 If sugars as ingested was considered to be

1 harmful, then that would be on the list. But if
2 they're not considered to be harmful or potentially
3 harmful, as ingested, then they should not be on the
4 list.

5 DR. BURNS: I understand that that's the
6 same piece on this. Now, how about the flipside? If
7 they produce toxic things, are they included on the
8 list?

9 DR. HATSUKAMI: If they produce it within --
10 if it's converted into a toxic element when they're
11 ingested, then I would assume that it's supposed to be
12 on the list.

13 DR. BURNS: Because the whole issue then of
14 nitrates and other things comes up. And then the
15 second question, which is if you have an ammoniated
16 compound that produces a change in the pH and it
17 changes the nicotine, is that a reason to put it on
18 the list or are we limiting it to compounds that are
19 toxic in and of themselves?

20 DR. HATSUKAMI: Dr. Husten wants to clarify.

21 DR. HUSTEN: I just wanted to remind the
22 committee of one of the parameters yesterday that we

1 requested the subcommittee, for the purposes of this
2 initial list, to focus on chemicals or chemical
3 compounds that are toxicants, carcinogens, or
4 addictive.

5 DR. HATSUKAMI: Dr. Hecht?

6 DR. HECHT: Responding to David's point, I
7 think that if there's good evidence that something can
8 produce a toxicant when it's ingested, then it should
9 be included.

10 DR. HATSUKAMI: Yes. Well, that would be my
11 -- Dr. Henningfield?

12 DR. HENNINGFIELD: Two clarifications. One,
13 we've mentioned addiction a couple of times, but my
14 understanding is that we're going to be deferring that
15 to the next meeting.

16 DR. HATSUKAMI: Right. Yes.

17 DR. HENNINGFIELD: And the with respect to
18 things like sugars, where there is a lot of evidence
19 that they say sugars converting to acetaldehyde,
20 that's well known enough that I don't know how you
21 could not mention it. But it doesn't mean we have to
22 exhaustively understand what everything is converted

1 into. But it seems that there will be a number of
2 things on the list that we couldn't leave off.

3 DR. BURNS: I'm trying to find the outer
4 boundary of that, Jack. There's lots of things that
5 produce acetaldehyde. There's lots of things -- and
6 there's natural sugars in the tobacco.

7 And so are we only talking about additives?

8 Once you open up the prospect that what
9 you're looking at is something in raw tobacco that has
10 the capacity to produce something bad in the burned
11 tobacco, I don't know of a list that allows us to do
12 that with any kind of -- certainly, not with the kind
13 of approach we've taken, which is that some other
14 entity has gone through this in a formal process and
15 made that kind of assessment.

16 DR. HATSUKAMI: Dr. O'Connor?

17 DR. O'CONNOR: The other thing I think we
18 need clarity on is are we talking about smokeless
19 tobacco products or are we talking about unburned, not
20 burned yet tobacco that's included in a cigarette or
21 other smoked products? I think that will eliminate
22 some of these other issues that we're talking about.

1 DR. HATSUKAMI: Corinne, do you have a
2 clarification on that?

3 DR. HUSTEN: Well, again, it's what from a
4 product is absorbed or inhaled or ingested and is
5 harmful as absorbed, inhaled, or ingested, if that's
6 helpful.

7 DR. HATSUKAMI: Dr. Farone?

8 DR. FARONE: Well, as a matter of process,
9 we covered smoking stuff. So now, if we want to cover
10 smokeless products, just smokeless, and we focus just
11 on that, then we have the same criteria; I mean, IARC
12 lists and their criteria. They handle things that are
13 carcinogens by ingestion just as well. It doesn't
14 matter where it comes from.

15 There are special indications for those
16 things which are carcinogenic only by inhalation. We
17 could remove those. And so we have pretty much the
18 same criteria. And if we just focus on smokeless,
19 like we did on smoke, then it should be a doable task
20 to go through the list and say, okay, if you ingest
21 these same materials that are in snus or in chewing
22 tobacco or in whatever, do they cause a problem, and I

1 think that's the simplest way to proceed.

2 DR. HATSUKAMI: I believe that that is our
3 charge.

4 Dr. Henningfield?

5 DR. HENNINGFIELD: One other thing just to
6 get on the record, for the guidance to NIDA for their
7 review, it might be pointed out to them that smokeless
8 tobacco is a consideration, because then you have
9 constituents, such as sodium bicarbonate, that I think
10 would not ordinarily be considered a toxicant in its
11 own right, but modifies the addictive potential of
12 smokeless tobacco by modifying the amount of free
13 nicotine and speed of delivery.

14 So NIDA should probably be looking at the
15 things that are on the list, but other things are
16 commonly used to modify free nicotine.

17 DR. HATSUKAMI: Good point.

18 Any other additional comments? So Dr.
19 Farone was correct. We will be taking a look at
20 smokeless tobacco products and what are some of the
21 harmful or potentially harmful constituents when they
22 are ingested.

1 People are clear on that?

2 Dr. Burns?

3 DR. BURNS: Just to be clear, are we talking
4 about things that have been identified in smokeless
5 tobacco?

6 DR. HATSUKAMI: I'm sorry. What was that?

7 DR. BURNS: Are we limiting the discussion
8 to compounds that have been identified in smokeless
9 tobacco or are we incorporating by reference
10 everything that we've identified from smoke? Because
11 the issue is that there's a much more limited
12 smokeless tobacco literature.

13 DR. HATSUKAMI: Yes. We are limiting to
14 smokeless tobacco.

15 DR. BURNS: Okay. So we need to have it
16 identified in smokeless tobacco in order to put it on
17 that list.

18 DR. HATSUKAMI: Yes.

19 DR. BURNS: Okay.

20 DR. HATSUKAMI: Yes.

21 Dr. Watson and Dr. Djordjevic, either one.

22 DR. DJORDJEVIC: Just for clarification, for

1 smokeless tobacco, when there was a review by IARC of
2 products from all over the world, they were included
3 and some of the products also include combustion
4 before they are used orally. That is why on the list
5 there are many PAHs.

6 So it's not that PAHs are there because it
7 was identified in smoke, but they were also identified
8 in tobacco. And yesterday we also heard a
9 presentation that in smokeless tobacco, fire-cured
10 tobacco type was used. So you have, also, as a
11 product of fire-curing, some PAHs in smokeless
12 tobacco. So it's not that it's only relevant to
13 smoke.

14 DR. HATSUKAMI: Dr. Watson?

15 DR. WATSON: Just picking up on what
16 Dr. Henningfield said. Particularly if we have sort
17 of a review by NIDA or some other authoritative body
18 looking at the addiction or things that modify
19 addictive properties of tobacco, the PAH modifiers, my
20 understanding is there are other compounds, too, that
21 are added, like silicylates, which may help the uptake
22 of nicotine.

1 If their charge could be expanded to look at
2 some of these things, at least the ones that are
3 commonly known -- this is sort of outside my area of
4 expertise. Maybe someone from the industry could
5 comment on this.

6 What other compounds or what other
7 considerations might we need to consider when we're
8 looking at addiction or uptake of nicotine or other
9 harmful agents?

10 DR. HATSUKAMI: All right. And that would
11 be something that we'll take a look at at the next
12 meeting. All right.

13 So are people clear now what our charge is?
14 Okay.

15 So the constituents that have been
16 highlighted in blue are the ones that have been
17 identified by different countries or different
18 agencies as being harmful or potentially harmful
19 constituents in smokeless tobacco products.

20 So what I thought is we'd go through this
21 list and decide whether we are in agreement with this
22 list. So the first constituent is ammonia.

1 I'm sorry. Yes, Dr. Husten?

2 DR. HUSTEN: I just want to clarify. I
3 believe that these lists are -- the C means that it's
4 in tobacco, and, again, given that other countries
5 follow different processes and stuff. But I wanted to
6 clarify that this did not mean it was in smokeless
7 tobacco products. These are in content. So they're
8 in tobacco.

9 DR. HATSUKAMI: So what we need to do is
10 decide whether they are also in smokeless tobacco.

11 Yes, Dr. Farone?

12 DR. FARONE: I don't know that we need to
13 really decide that, because it is tobacco that makes
14 smokeless. The point that Mirjana made, I mean, take
15 that into consideration.

16 If it's been found there, I think then it's
17 included, by what we were discussing before. Take,
18 like, ammonia. There's soluble ammonia in all
19 tobacco. So ammonia is there. And so, therefore, we
20 can go down the list with that kind of logic and then
21 if we have to add or subtract, we can do it.

22 DR. HATSUKAMI: Right. Yes.

1 So should we proceed? All right.

2 Dr. Hecht?

3 DR. HECHT: Ammonia is a gas. It's not in
4 tobacco. It's silly to have ammonia in tobacco. It
5 would evaporate. So maybe ammonium salts or something
6 like that.

7 DR. HATSUKAMI: Any comments?

8 Yes, Dr. Farone?

9 DR. FARONE: Yes. When you say ammonia,
10 soluble ammonia, that's, obviously, what -- what is
11 meant is they convert it after they extract it. So
12 it's measured as ammonia, but it's not ammonia in the
13 tobacco. Correct.

14 DR. HATSUKAMI: So I guess I'm not sure what
15 you're --

16 DR. FARONE: Well, it's ammonia. There are
17 methods for determining the ammonia in tobacco, but it
18 is not, as Dr. Hecht just pointed out, literally
19 ammonia. It's bound. So it is bound to something
20 else.

21 So the question is, do you say all ammonium
22 salts or ammonia as extracted? I mean, I think that's

1 what he's bringing up, which is correct. But it is
2 normally listed as extractable ammonia.

3 DR. HATSUKAMI: Dr. Watson?

4 DR. WATSON: Just basically building on what
5 Dr. Farone said. I think we are talking about
6 ammonium salts and the filler and depending on the
7 analytical technique you're using to analyze these,
8 you can prep the sample so it ends up as soluble
9 ammonia and you can analyze it that way or depending
10 on the technique, you can analyze for ammonium ion, if
11 you're using something, say, for instance, ion
12 chromatography.

13 So I think the point is well taken. A gas
14 species probably isn't expected to be there. But what
15 we're looking at here probably is the contribution
16 from these ammonium salts.

17 DR. HATSUKAMI: Dr. Burns?

18 DR. BURNS: Just to be clear as to why it's
19 on the list, it's on the list for cigarette smoke,
20 because it's a respiratory irritant. Here, we're
21 talking presumably about its role as a facilitator of
22 nicotine as opposed to its primary toxicity directly.

1 DR. HATSUKAMI: So maybe this is something
2 that we should punt to the next meeting. Okay.
3 Deferred. All right.

4 Anabasine and anatabine. I think those are
5 also nicotine. Yes. So I think we'll defer that, as
6 well.

7 Arsenic, include that. Okay.

8 Benzo[a]pyrene, include that. Okay.

9 Dr. Burns?

10 DR. BURNS: Using the same -- I mean, since
11 the principal source of benzo[a]pyrene is combustion
12 during curing as opposed to something intrinsic in the
13 tobacco itself, we probably need to include the rest
14 of Steve's list of PAHs in order to be consistent.

15 DR. HATSUKAMI: Okay. So we'll add that,
16 the rest of Dr. Hecht's PAHs. Cadmium.

17 DR. LAUTERBACH: Question.

18 DR. HATSUKAMI: Yes, Dr. Lauterbach?

19 DR. LAUTERBACH: Question for Dr. Hecht.

20 You mean the list for smokeless tobacco, you
21 mean the list of compounds in Dr. Stepanov's paper.

22 DR. HECHT: Only those that are Group 1, 2A

1 or 2B.

2 DR. HATSUKAMI: Cadmium.

3 Dr. Watson, did you have a -- okay.

4 Cadmium; yes. Okay. Chromium; yes.

5 Okay. Eugenol.

6 Dr. Hecht?

7 DR. HECHT: There's crotonaldehyde in
8 smokeless tobacco.

9 DR. HATSUKAMI: Crotonaldehyde. Okay. So
10 yes to crotonaldehyde.

11 DR. BURNS: Is there evidence for eugenol
12 being toxic in oral administration? I know that there
13 is for respiratory inhaling and there may be some data
14 on nicotine. But is it toxic? Okay.

15 DR. HATSUKAMI: What was that, Dr. Hecht? I
16 couldn't hear you. What was that?

17 DR. HECHT: I think there's data on toxic
18 effects of eugenol by oral administration. I've
19 forgotten exactly what they are, but I'm pretty sure
20 there are.

21 DR. HATSUKAMI: Maybe we can get some
22 references for that.

1 DR. HECHT: Yes.

2 DR. HATSUKAMI: So we'll put that on -- yes?

3 DR. O'CONNOR: Did we put acetaldehyde on
4 the smokeless list, as well? Because I think it's
5 also a component in there.

6 DR. HATSUKAMI: Yes. Let's see. Okay. All
7 right.

8 So the eugenol, why don't we get the
9 references for that and then we'll -- but for right
10 now, it's yes. We can defer with references.

11 Glycerol. Formaldehyde. Sorry about that.

12 Formaldehyde; yes. Glycerol. No? Yes.

13 DR. HECHT: Why is glycerol on the list at
14 all? I thought we took glycerol off.

15 DR. HATSUKAMI: We took it off as a -- this
16 is a list that was developed based upon the background
17 information that was provided to you. And so there
18 are some countries that had listed glycerol as being
19 harmful or potentially harmful.

20 So we just wanted to make sure that it's not
21 people --

22 DR. FARONE: Volume 89 of IARC, which was

1 part of what was passed out, has some of these and it
2 tells you what kind of tobacco it was found in. So
3 formaldehyde, acetaldehyde and crotonaldehyde are all
4 there. I don't know if we want to maybe look at that
5 list or print it out. It's table 3, page 58.

6 DR. HATSUKAMI: I think we may go back to
7 that. Why don't we finish up with this list first and
8 then we'll go back to it?

9 DR. FARONE: Okay.

10 DR. BURNS: Just to be clear, a lot of the
11 things that are listed there for contents are not on
12 those lists, because they were designated as toxic.

13 DR. HATSUKAMI: That's right.

14 DR. BURNS: They are on the list because
15 they were designated as things they wanted to measure
16 to understand how the product was changing. So we
17 need to be clear.

18 DR. HATSUKAMI: Absolutely. You're right.
19 Okay.

20 So that's a no, right? Okay. Lead; yes.

21 Okay.

22 We'll skip the menthol.

1 Mercury. No? Did someone say no?

2 DR. BURNS: There's no question that oral
3 ingestion of mercury in food stuffs is a substantive
4 issue, and the fact that it may not be present in the
5 testing that has been done of U.S. products in
6 substantial amounts doesn't guarantee that it won't
7 be.

8 DR. HATSUKAMI: So basically, you think it
9 should be on the list then.

10 DR. BURNS: Yes.

11 DR. HATSUKAMI: Does everybody agree with
12 that?

13 [No response.]

14 DR. HATSUKAMI: No objections? Okay.

15 Let's see. That's an addictive agent. N-
16 nitrosoanatabine.

17 DR. HECHT: Why is that there? I thought we
18 dropped nitrosoanatabine yesterday.

19 DR. HATSUKAMI: Okay. We can say no. And
20 nitrosoanabasine, as well. No?

21 DR. HECHT: No, it's yes.

22 DR. HATSUKAMI: Okay. Yes. Yes on that

1 one.

2 DR. HECHT: Wait a minute. No, no, no.

3 Nitrosoanatabine is no.

4 DR. HATSUKAMI: This is no.

5 DR. HECHT: We dropped that yesterday,
6 because it's not carcinogenic.

7 DR. HATSUKAMI: Yes, that's correct.

8 Nickel.

9 DR. HECHT: Wait a minute.

10 Dimethylnitrosamine. Nitrosodimethylamine.

11 DR. HATSUKAMI: Okay. Yes on N-
12 nitrosodimethylamine.

13 DR. HECHT: Yes.

14 DR. HATSUKAMI: It's on the IARC list for
15 oral tobacco, yes.

16 Dr. Farone, and then Dr. Watson.

17 DR. FARONE: Yes. It's not only on the
18 list, but it's found in smokeless products, according
19 to IARC.

20 DR. HATSUKAMI: Okay. Yes.

21 Dr. Watson?

22 DR. WATSON: Can we scroll the list back

1 down? I think there might have been a "no" entered by
2 myosmine, which should be deferred, I believe.

3 DR. HATSUKAMI: I'm sorry. Myosmine? Yes.
4 Okay.

5 DR. WATSON: I don't want the error to go in
6 there and have it dropped off the list for a typo.

7 DR. HATSUKAMI: That would be yes for
8 addiction.

9 DR. WATSON: That one I think we would defer
10 for additive, yes. So defer for now.

11 DR. HATSUKAMI: Yes. That should have said
12 deferred. Yes. Sorry. All right.

13 Nickel; yes. Okay. That's a yes.

14 Nicotine, obviously, is a yes, but that's
15 going to be deferred.

16 Nitrate. Well, why don't we just put yes on
17 that one? We have convincing evidence.

18 Nitrate; that was an issue that we talked
19 about. Yes. Yes.

20 NNK?

21 DR. HECHT: We have to put in nitrite in
22 addition to nitrate.

1 DR. HATSUKAMI: Put a column in and put
2 nitrite.

3 DR. HATSUKAMI: NNK, I would think yes.
4 NNK, everybody agrees, I would imagine.

5 NNN? Everybody is in agreement with NNN.
6 Okay. Nornicotine should be deferred.

7 DR. HECHT: Nitrosopyrrolidine.

8 DR. HATSUKAMI: Yes? Yes. Okay. Yes for
9 nitrosopyrrolidine. Nornicotine should be deferred.
10 Any of the other -- propylene glycol, I think we --
11 no. No. Okay.

12 Selenium; yes. Okay. Yes.

13 Sodium propionate. No?

14 DR. HECHT: I thought we dropped that.

15 Why is that on there?

16 DR. HATSUKAMI: Basically, we're just -- I'm
17 sorry, Steve. There wasn't enough time to go back and
18 drop the ones that we had dropped before. We were
19 just using a list that was created through summaries.
20 So it is repetitive. We understand that. But there
21 was just too little time to develop a list.

22 Sorbic acid I think we dropped, as well.

1 Triacetin.

2 You're going to have to use your mic, Dr.

3 Lauterbach.

4 DR. LAUTERBACH: I don't believe triacetin
5 is used in smokeless tobacco products.

6 DR. HATSUKAMI: Okay. So drop that. All
7 right. Drop that.

8 And triethylene glycol. No? No. Okay.

9 We want to make sure we didn't miss
10 anything. So let's just go through the ones that are
11 in white. Probably not acetone.

12 Any of those other constituents that should
13 be included, the ones in white?

14 DR. FARONE: I think we could facilitate, if
15 you could print table 3 of --

16 DR. HUSTEN: We are trying to get that
17 printed right now.

18 DR. FARONE: Okay. Because then we could
19 just compare it and add the things that are on there
20 that we missed.

21 DR. HATSUKAMI: So meanwhile, Dr. Farone,
22 since you have the list, you can let us know ones that

1 we have not included on here; any of the constituents
2 in white that we should have included.

3 [No response.]

4 DR. HATSUKAMI: Okay. No comments.

5 Dr. Farone, you're still checking.

6 DR. FARONE: I'm trying to check back and
7 forth. It's kind of difficult. I see some that are
8 here that aren't on the list at all.

9 DR. HATSUKAMI: So why don't you read those
10 off to us?

11 DR. FARONE: Coumarin is one.

12 DR. HATSUKAMI: Coumarin.

13 Do you people approve of coumarin? Any
14 objections to adding coumarin on the list?

15 DR. FARONE: It's a Group 3. We may not
16 want to --

17 DR. LAUTERBACH: One of the problems here is
18 this IARC review does not give the primary source. So
19 it's hard to see what this is doing with reference to
20 any sort of contemporary products when we do not know
21 where the references are.

22 I think some of these references come back

1 to literatures or articles that were written in 1986
2 and '87 and may have absolutely no relevance to
3 commercial practice today.

4 DR. HATSUKAMI: Dr. Farone?

5 DR. FARONE: The reference here is to 2000.

6 DR. LAUTERBACH: That's the IARC volume.

7 DR. FARONE: Yes, Volume 77. But if we
8 looked in the IARC Volume 77, we would find the
9 reference.

10 DR. HATSUKAMI: I think in our previous
11 deliberations, Dr. Lauterbach, we decided to include
12 them on the list to be comprehensive. And if there is
13 any evidence to the contrary, then they could be
14 modified. The list can be modified.

15 Any objections to coumarin being on the
16 list?

17 [No response.]

18 DR. HATSUKAMI: Okay. Dr. Farone?

19 DR. FARONE: Ethyl carbamate was the next
20 one they have, a Group 2A.

21 DR. HATSUKAMI: Okay. Ethyl carbamate.

22 Any objections to that?

1 [No response.]

2 DR. HATSUKAMI: Okay. Next product?

3 DR. FARONE: Well, the next set are the
4 volatile nitrosamines. I think the
5 nitrosodimethylamine, we had that, I think. So we had
6 the N-nitrosodimethylamine. I think we had that on
7 our list. The N-nitrosopyrrolidine, the N-
8 nitrosopiperidine, the N-nitrosomorpholine, and the N-
9 nitrosodiethanolamine are the ones that they found in
10 smokeless. I don't know if they were all on the list
11 before.

12 DR. HECHT: They should all be on the list.

13 DR. HATSUKAMI: Okay.

14 DR. HECHT: I mean, we have to go through
15 this list and make sure that we --

16 DR. HATSUKAMI: Let's go back. Let's go to
17 the other list.

18 Could you repeat that, Dr. Farone, in terms
19 of what you had identified?

20 DR. FARONE: Maybe the best way -- I don't
21 know -- we could put in a reference afterwards -- if
22 we just use the abbreviations. Maybe that's the

1 better way for the typing right now.

2 N-nitrosodimethylamine is the first one, and
3 I think we had that.

4 DR. HATSUKAMI: Yes. We already had that.

5 DR. FARONE: Then the N-nitrosopyrrolidine.

6 DR. HATSUKAMI: That's it?

7 DR. FARONE: No. N-nitrosopiperidine.

8 DR. HATSUKAMI: I think maybe the best thing
9 to do, Dr. Farone, is to just read the list and we can
10 just go through them and ones that we are not going to
11 be actually agreeing with we can take off the list.
12 They can add this on later, because this is taking too
13 much time.

14 So if you can just go ahead and read that
15 list, then we can agree to include it or not to
16 include it.

17 DR. FARONE: Okay. Well, I already read the
18 volatile N-nitrosamines before.

19 Do you want me to read the --

20 DR. HATSUKAMI: Okay. No, no. You don't
21 need to read that.

22 DR. FARONE: Then there's the N-nitrosamine

1 acids, which are next. The N-nitrososarcosine, the
2 3,N-methyl -- I can't quite see that. 3,N-
3 methylnitrosamine propionic acid is the next one.
4 4,N-methylnitrosamine butyric acid. Nitroso -- looks
5 like there -- I can't quite see it. 4-carboxylic
6 acid. So it's nitroso-azetidine-4-carboxylic acid.

7 Then we have the TSNAs. We have NNN, NNK,
8 and NNAL. And here, they listed NAB. Then arsenic,
9 nickel compounds, and then they list the radio
10 elements, polonium-210, uranium-235 and 238, and
11 beryllium.

12 DR. HATSUKAMI: Any objections to any of
13 those compounds or constituents being on the list?

14 Dr. Lauterbach?

15 DR. LAUTERBACH: The last several compounds
16 that Dr. Farone read off, there's no reference given
17 in the monographs. There's no carcinogenic
18 classification given on the last three. And I don't
19 see why we're putting these in when there's no data
20 here really in terms of classification as these things
21 being toxic.

22 DR. HATSUKAMI: Yes, Dr. Farone?

1 DR. FARONE: Well, I don't know. The radio
2 elements, they're all Group 1. That's what it says.
3 And what they say is the evaluation of internally
4 deposited alpha particle-emitting radionuclides. So
5 it seems there is a group classification.

6 It looks like there's designations for each
7 of the ones that I read in animals or in humans.

8 DR. HATSUKAMI: Dr. Lauterbach?

9 DR. LAUTERBACH: My table here shows the
10 last three nitrosamino acids as no IARC evaluation or
11 carcinogenicity, and there's really no reference in an
12 IARC manual, monograph after them.

13 Unfortunately, what we don't have here, if
14 you go to the full IARC volumes, the table of all the
15 footnotes which go back to the literature references
16 and the original research.

17 So what we have here is basically just a cut
18 without all the footnotes.

19 DR. HATSUKAMI: Dr. Farone?

20 DR. FARONE: Yes. He was looking at a
21 different -- the last four I took as being the radio
22 elements. What he's referring to is the 3,N-

1 methylnitrosamine propionic acid, the butyric acid,
2 and the nitrosoazetadine-4-carboxylic acid.

3 They have the ranges and I don't know if
4 they're on the other list, but there are no
5 designations on this particular list as to their IARC
6 group.

7 DR. HECHT: Because they weren't evaluated.
8 They haven't been evaluated by IARC. So are we going
9 to include them or not? MNPA is a weak carcinogen.
10 MNBA and nitrosoazetadine and carboxylic acid as far
11 as I know, are inactive. But there's not much data.
12 MNPA has only been tested once, as far as I know.

13 Mirjana?

14 DR. DJORDJEVIC: I think there was research
15 done in Heidelberg in the cancer center there, where
16 there was a group by Preussmann, Spiegelhalder and
17 others. But, also, there was lots of research by the
18 Bartsch group on this group of compounds, but they
19 were not evaluated, you were right, for the
20 carcinogenicity and classified.

21 But there are many other toxicity studies
22 and bioassays done with these compounds and they were

1 designated as carcinogenic constituents.

2 DR. HATSUKAMI: So do you think that there's
3 sufficient evidence to include it on the list as a
4 result?

5 DR. DJORDJEVIC: As Steve said, they were
6 not evaluated for sufficient evidence, but there is
7 literature on them and the tests, the toxicological
8 testing.

9 DR. HATSUKAMI: Dr. O'Connor?

10 DR. O'CONNOR: Maybe we should check them
11 against the report on carcinogens in the U.S., similar
12 to what we did to the smoke constituents yesterday.
13 For ones that weren't necessarily on the IARC list,
14 they may be on other lists, EPA or ASTAR.

15 Somebody else may have done the evaluation
16 and we can check it against that, as well.

17 DR. HATSUKAMI: I don't believe we have
18 those lists, if they do have such a list.

19 Do we?

20 DR. O'CONNOR: They're easy enough to look
21 up.

22 DR. DJORDJEVIC: Just a point about these

1 acids. They are kind of more difficult to analyze
2 than, let's say, other nitrosamines, either volatile
3 or TSNAs. So very few labs have the capacity to do
4 them, but they are, obviously, present in smokeless
5 tobacco. And there are studies to point out today
6 toxicity and carcinogenicity.

7 DR. HATSUKAMI: So I'm trying to get a sense
8 of whether the -- how is the committee feeling towards
9 including them or excluding them from the list?

10 Dr. Hecht?

11 DR. HECHT: It depends what our criteria
12 are. If our criteria are that they have to have been
13 evaluated by IARC or one of the other bodies, then we
14 would not include them, unless there's something out
15 there that we're not aware of, because far as I know,
16 IARC hasn't evaluated these.

17 DR. HATSUKAMI: Perhaps what we should do is
18 defer those constituents and see whether there are any
19 other agencies that have evaluated them. Is that what
20 you're saying, Dr. O'Connor?

21 DR. O'CONNOR: Yes.

22 DR. HATSUKAMI: And then we can decide at a

1 later time whether to include them or not.

2 DR. DJORDJEVIC: I have one comment. On
3 this list, we also have NNL and it wasn't evaluated by
4 IARC for carcinogenicity. But we know, through many
5 of your studies, Dr. Hecht, that that is, after NNK,
6 the most potent carcinogen found in tobacco.

7 So we have NNL on the list, but it is not
8 evaluated and we know that it is carcinogenic.

9 DR. HATSUKAMI: Mirjana, you're saying still
10 include them on the list, even though it has not been
11 evaluated by IARC.

12 DR. HECHT: Yes. I mean, NNL has got to be
13 in.

14 DR. HATSUKAMI: Sure. If we have sufficient
15 rationale to include them, I think that's fine. Okay.
16 So we'll still retain NNL. All right.

17 DR. HECHT: Isn't there one report of NNL in
18 smoke? Didn't you guys do that?

19 DR. WATSON: We've measured it, but only the
20 physical presence, and no toxicity testing. But it is
21 present in very low levels in cigarette smoke.

22 DR. HECHT: So it should be on the smoke

1 list, NNL.

2 DR. HATSUKAMI: Right. So we did retain
3 that.

4 DR. HECHT: No. It's not on the list.

5 DR. HATSUKAMI: Yes. No. We decided to put
6 it on the list, NNL.

7 DR. HECHT: Both tobacco and smoke.

8 DR. HATSUKAMI: Oh, in smoke.

9 DR. HECHT: Yes.

10 DR. HATSUKAMI: No. We did not include that
11 on smoke. I'm sorry.

12 DR. HECHT: That's what I'm telling you,
13 Dorothy.

14 DR. HATSUKAMI: So we should include that in
15 smoke.

16 DR. HECHT: Yes.

17 DR. HATSUKAMI: Okay. Any objections to
18 that?

19 Mirjana?

20 DR. DJORDJEVIC: I don't have objections to
21 that. But if we are finished with the IARC list and
22 we are continuing, I want to bring to the discussion

1 what we mentioned yesterday, aflatoxin. So that is a
2 carcinogen which could be found in tobacco and it is
3 already on the list of the European Smokeless Tobacco
4 Council, and they even set some upper limits for it.
5 So we should consider that one on the list.

6 DR. HATSUKAMI: Okay. So let's have a
7 discussion on that, aflatoxin.

8 Should that be on the list for smokeless
9 tobacco?

10 DR. HECHT: Yes, absolutely.

11 DR. HATSUKAMI: All right. We'll include
12 that on the list. All right.

13 So thus far, what we've done is we've gone
14 through the summary list that was provided to us by
15 FDA. We've gone through the IARC list. We've added
16 aflatoxin to the list.

17 Is there any other method that we should be
18 identifying the constituents for the harmful and
19 potentially harmful constituents for smokeless
20 tobacco?

21 Yes, Dr. Hecht?

22 DR. HECHT: We didn't add the polycyclics,

1 other than benzopyrene.

2 DR. HATSUKAMI: That's right. So we should
3 go through your list that you provided us yesterday
4 and make sure that we captured everything.

5 So the polycyclics, any of those that we
6 should add for smokeless tobacco?

7 DR. HECHT: Benzanthrane.

8 DR. HATSUKAMI: Okay.

9 DR. HECHT: Benzo(b, j and k)fluoroanthene.
10 Chrysene.

11 DR. HATSUKAMI: Could you just hang on a
12 second? Okay.

13 DR. HECHT: Chrysene.
14 Dibenz(a,h)anthracene. Indenopyrene. That's it.

15 DR. HATSUKAMI: Okay. Any objections?

16 [No response.]

17 DR. HECHT: Naphthalene.

18 DR. HATSUKAMI: Wait a second. We just want
19 to make sure everybody -- no objections.

20 Okay. Go ahead.

21 DR. HECHT: We did the nitrosamines, right?

22 DR. HATSUKAMI: Yes.

1 DR. HECHT: I think that's it.

2 DR. HATSUKAMI: Okay. Any additional
3 comments? All right. So far, we have a list for
4 smoke emissions and we also have a list for the
5 smokeless tobacco.

6 So I think what we plan to do is -- they're
7 going to be putting together a cleaned-up list for us,
8 a consolidated list for us, so that we can take a look
9 at the various constituents that we've identified. I
10 believe they're going to do that after lunch -- during
11 lunch. Sorry. During lunch, not during the meeting,
12 during lunch.

13 I guess at this point in time, we can either
14 take a break -- I think we need that cleaned-up list
15 before we can start looking at what methods -- whether
16 there are methods to assess some of the constituents
17 that we have identified.

18 So I think what we should do -- go ahead.

19 DR. LAUTERBACH: When you get through with
20 what you're saying, I'd like to make some general
21 comments about analyses and methods that are not
22 compound-specific or method-specific, just some

1 general observations.

2 DR. HATSUKAMI: That's fine. We can reserve
3 that to prior to our discussion about methods, assay
4 methods, or do you want to --

5 DR. LAUTERBACH: I can do it now, if you're
6 done.

7 DR. HATSUKAMI: Dr. Heck?

8 DR. HECK: I just had one small comment with
9 regard to aflatoxin, which we've passed on. We want
10 to check the spelling of aflatoxin on the list before
11 we print it. Is it A-F-L-A? And I think we're
12 concerned about aflatoxin B1.

13 There's a whole family of aflatoxins,
14 aflatoxin Gs. B1 is really the potent carcinogen. If
15 there's no objection, we might want to specify AFB1 is
16 what we intend.

17 DR. HATSUKAMI: Okay.

18 Any other comments? If not, Dr. Lauterbach,
19 you can make your comment.

20 DR. LAUTERBACH: Thank you. Just in terms
21 of the whole methods and analytes, whether we're doing
22 one analyte or 100, I just have this concern that we

1 may not be working all together.

2 If we're going to have this program be
3 meaningful, we can't have a wall between the FDA
4 scientists on one side and everybody else on the other
5 side. I understand that's been typical of some of the
6 top lab reg things, where knowledgeable people have
7 been excluded from the discussion because of
8 assertions about their financial background and of
9 their corporations or whatever.

10 We can't have that. We have to have open
11 dialogue between those of us that may be representing
12 clients or companies and the FDA scientists. I think
13 this is very clear, and we really should have a
14 commitment on that now that we can have this open
15 dialogue going further.

16 Then, again, if the CDC or Center for
17 Tobacco Products have any laboratories, they need to
18 be basically ISO-17025. They need to have the
19 certifications for the methods they're running, the
20 qualified staff, equipment.

21 The other thing we need, desperately need,
22 from CTP and CDC personnel is participation in

1 international standards organizations that affect
2 these methods. We have, as part of ANSI -- this has
3 not to do with industry -- it runs out of ANSI. We
4 have an ISO tag in this country that helps essentially
5 cast the votes on international standards, and we
6 really need the participation of scientists from CDC
7 and CTP on that.

8 I think the other thing, also, on a slightly
9 related note, if we're going to be collecting all
10 these data, 80-100 analytes per brand style or
11 whatever, someone needs to figure out how we're going
12 to interpret those data, what the criteria for a true
13 difference between two products are, those criteria.
14 Otherwise, we're going to be like Canada and Brazil.
15 We're going to collect reams of data and nothing is
16 going to happen to them.

17 It takes a lot of skill and training to be
18 able to interpret the data and figure out what are
19 real differences between products and what is just
20 random variation in the analyticals.

21 DR. HATSUKAMI: I think that our current
22 charge was primarily to identify the harmful or

1 potentially harmful constituents, but your comments
2 certainly are noted.

3 Any other things? So I think what we'll do
4 is we'll break for lunch early so that we can get
5 these lists consolidated, and I think we should be
6 back by 12:30.

7 I need to read the script. I'm sorry.

8 We will now break for lunch. Committee
9 members and consultants, please remember that there
10 must be no discussion of the meeting topic during
11 lunch either amongst yourselves, with the press, or
12 with any members of the audience.

13 Thank you, and we'll see you back here at
14 12:30.

15 (Whereupon, at 10:55 a.m., a lunch recess
16 was taken.)

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A F T E R N O O N S E S S I O N

(12:42 p.m.)

DR. HATSUKAMI: I think we'll go ahead and get started. So now we have a list of the harmful and potentially harmful constituents in tobacco products, including tobacco smoke. We have it listed by inhaled from smoke or absorbed or consumed from tobacco products.

So what I'd like to do now is to go down the list. If there are any objections to any of the items that we've listed, please raise them. But what I'd also like to do is to go ahead and discuss whether there are methods available to make the assessment of the constituents.

Yes?

DR. LAUTERBACH: Clarification. I thought deciding on carcinogens, it had to be IARC 1, 2A or 2B, but I believe some number 3s slipped in here or were mentioned.

Could someone clarify that, please?

DR. HATSUKAMI: You're talking about the NNL? No?

1 DR. HECHT: There are a couple of number 3s
2 on the list.

3 DR. HATSUKAMI: Why don't we identify them
4 when we get to them and have some discussion on them?
5 Would that be okay? As we proceed down the list, if
6 you see them, please identify them and we can have a
7 discussion. Okay.

8 Now, these are not divided up into whether
9 they are carcinogens or whether they're toxicants or
10 addictive constituents. So just to let you know that.

11 So acetaldehyde, there is a method
12 available.

13 DR. LAUTERBACH: Comment, please.

14 DR. HATSUKAMI: Yes, Dr. Lauterbach?

15 DR. LAUTERBACH: I think we have to be very
16 careful on what we claim is a method.

17 Is it acetaldehyde in smokeless tobacco or
18 is it acetaldehyde in smoke, and whose method, and, if
19 it's in smoke, under what smoking conditions?

20 DR. HATSUKAMI: So that's actually what we
21 were going to do in the next meeting. We're going to
22 be talking about what method.

1 DR. LAUTERBACH: Okay. But then let's not
2 put it up here now as saying there's a method, when I
3 don't think there is.

4 DR. HATSUKAMI: You don't think there's a
5 method for acetaldehyde analysis.

6 DR. LAUTERBACH: I don't believe there's one
7 that's been fully validated across enough laboratories
8 to say it's correct or not, and definitely not for
9 smokeless.

10 DR. HATSUKAMI: Dr. Farone?

11 DR. FARONE: Yes. Well, I thought -- and
12 just a process question, yes. We're not in the
13 business of validating methods. I think what the
14 objective of the exercise was to determine whether or
15 not reasonably a method exists and then I think the
16 discussion of validation of methods was beyond really
17 the scope of what we were asked to do.

18 If there's no method that anybody knows
19 about, it probably shouldn't be on the list. If there
20 are methods that have been used, the issue of whether
21 that method is going to be acceptable to FDA down the
22 road, I don't know that that was part of our charge.

1 DR. HATSUKAMI: The charge today is not to
2 determine whether those methods are validated or not.
3 The charge right now is to know whether there is a
4 method for assessment.

5 DR. LAUTERBACH: But if a method is not
6 validated, it's not a method. You can say there's a
7 technique available, but unless you have a method
8 that's been validated across laboratories and you have
9 good statistics on it, it's not a method.

10 DR. HATSUKAMI: Dr. Watson, and then Dr.
11 Henningfield.

12 DR. WATSON: My understanding is what we're
13 trying to look at today is -- if we're going to make
14 recommendations of things that should be looked at,
15 that we want to at least make sure the analytical
16 technology exists to reasonably try to tackle these
17 problems.

18 So I think that's sort of the charge today,
19 not really -- because we're going to have to get into
20 the nitty-gritty at some point about exactly how we're
21 going to measure these, how we're going to do sample
22 preparation, and that will be somewhat dependent on

1 what FDA, in their mission, they need to do and what
2 quality of data they need in terms of setting limits
3 or whatever it is, how they're going to use this.

4 I just wanted to mention one quick sort of
5 disconnect yesterday. Several of the speakers
6 yesterday talked about methods, talked about a high
7 degree of variability and why some of these things
8 basically need to be looked at and seriously
9 considered, comparing one analyte versus another and
10 why there's variability and where this all comes from.

11 The FDA, I'm sure, is in the regulatory
12 business. CDC is not in the regulatory business. My
13 lab mainly does research. And so I'm not an expert in
14 this area, but, presumably, FDA does have people that
15 are experts in sort of how does one sort of mandate
16 what's a satisfactory test.

17 But when we were talking about these
18 analytical capabilities, sort of a question that came
19 to my mind is there are a variety of places where data
20 is currently being generated, commercial labs, for
21 instance. We have Labstat. If I call Bill Rickert or
22 Richard Higby or Helen Taylor on the phone for

1 Labstat, Arista or Filtrona -- these are the only ones
2 I know, off the top of my head, not saying that these
3 are the only tobacco labs out there. But if I ask
4 them to run a battery test, like a Hoffmann list, on
5 100 brands of cigarettes, they'll basically send me a
6 quote and I'll pay and they'll do the analysis and
7 I'll get the data back.

8 So at least one of them, Labstat, is
9 involved in the regulatory process for Health Canada.
10 So maybe as we're sort of asking for guidance from
11 somebody like NIDA on addiction, maybe we should sort
12 of see how, in a regulated environment such as Canada,
13 how they came upon the decision for using a commercial
14 lab and what criteria goes into the decision about the
15 type of data they're getting feedback on.

16 So that's just to throw that out for comment
17 for the next meeting. That would be very helpful to
18 get that guidance on what is the best way to approach
19 this problem.

20 DR. HATSUKAMI: That's a good idea.

21 DR. LAUTERBACH: I think what my concern is
22 is that for the small business tobacco folks, we may

1 have to use several laboratories to get our things
2 done and when you start going across laboratories -- I
3 agree, if you are doing Health Canada work and all
4 your samples are run at one laboratory and you don't
5 have to compare your results with those at other
6 laboratories, I agree that there is a Health Canada
7 method and Dr. Rickert has the laboratory. I don't
8 disagree on that.

9 I think the question comes in, do we have a
10 method that we can operate over multiple laboratories
11 and get satisfactory results. If we want to say
12 there's a Health Canada method for acetaldehyde in
13 tobacco smoke, I'm agreeable to that one.

14 DR. HATSUKAMI: I think that our charge
15 right now is not to really determine whether we have
16 the capacity to do this, but really to know -- to
17 determine whether there are the technologies available
18 to assess these constituents.

19 So I understand your concern, Dr.
20 Lauterbach, but at this point in time, I think we
21 should just stick with what our charge is.

22 DR. LAUTERBACH: If you say technology is

1 available or if you want to put down a Health Canada
2 number, that's fine. But to say there's a general
3 method that we can use here, and particularly with
4 smoking and the smoking conditions not defined, that's
5 where it gets dicey.

6 DR. HATSUKAMI: So you feel comfortable if
7 we change the method available to technology
8 available. Is that all right with the rest of the
9 committee?

10 DR. BURNS: Well, is that consistent with
11 our charge?

12 DR. HATSUKAMI: Yes.

13 DR. BURNS: Does the charge specify the word
14 "methodology" or not?

15 DR. HUSTEN: Since we are required to
16 develop a list and to develop that list with
17 quantities by brand and sub-brand, I think the initial
18 question is whether quantities can be obtained.

19 DR. BURNS: I'm just asking the question as
20 to whether the methodology was actually in the -- you
21 gave us three questions. I don't have them.

22 DR. HUSTEN: I will have to look at my

1 slides.

2 DR. HATSUKAMI: Dr. Henningfield?

3 DR. HENNINGFIELD: A lot of this is beyond
4 this meeting. The word "method" is in the questions
5 to the committee. I think too much is being made out
6 of whether we use the word "method" or "technology."
7 "Method" is a large umbrella in science and
8 assessment.

9 DR. HUSTEN: It says are there established
10 analytic methods, basically.

11 DR. HATSUKAMI: So we'll put the analytic
12 method.

13 DR. HENNINGFIELD: My own feeling is that
14 where people on the committee feel there is enough to
15 move forward today, we move forward; and, at another
16 time, we will move forward even further on the
17 strength of the methods, where more work needs to be
18 done, and, ultimately, that won't be resolved in this
19 committee either. It'll be resolved at FDA.

20 DR. HATSUKAMI: Dr. Farone?

21 DR. FARONE: The way I look at it, we
22 haven't been asked to decide what methods FDA should

1 publish in the book by measuring these. That will
2 come later. They will be posted. People will have
3 time to respond to what method they suggest, whether
4 it's an EPA method or a new method or whatever.

5 So it's just a question of whether it's
6 reasonable to get numbers, the way I heard the
7 question; that is, quantitative information about the
8 relative differences between these materials and one
9 product to another. That's the way I see it.

10 DR. HATSUKAMI: Do we need further
11 discussion?

12 [No response.]

13 DR. HATSUKAMI: Okay. So let's proceed.
14 Acetaldehyde, we have an analytic method.

15 Acetamide, do we have an analytic method for
16 that? Dr. Watson, Dr. Hecht, do we know?

17 DR. HECHT: I don't know.

18 DR. WATSON: Hang on a second. I'm looking
19 here very quickly.

20 Where does it fall? Is it a carcinogen?

21 DR. HATSUKAMI: Pardon?

22 DR. WATSON: What class is it?

1 DR. HATSUKAMI: What class is acetamide, Dr.
2 Hecht?

3 DR. HECHT: I don't remember.

4 DR. WATSON: This list I have, I'm looking
5 through real quickly. This is sorted by
6 cardiovascular effect, cancer effect. So I was just
7 trying to find it, quickly.

8 DR. HECHT: It's Group 2B.

9 DR. HATSUKAMI: But what class?

10 DR. HECHT: It's a carcinogen. It's a
11 volatile -- it's a miscellaneous organic compound,
12 relatively volatile.

13 DR. WATSON: I don't have any specific
14 information on that here. We'll have to maybe defer
15 that. I would assume methods do exist, but I can't
16 quote a reference.

17 DR. HATSUKAMI: We can put a question mark
18 on there, then. Okay. Acrylamide?

19 DR. HECHT: What happened to acetone?

20 DR. HATSUKAMI: Acetone, I think there's
21 already been methods, analytic methods that are
22 available. We actually put yeses on the constituents

1 which were on the summary list that had methods
2 indicated. It was on the summary background material
3 that you received.

4 So we just didn't want to repeat what was
5 already handed out to you. So that's why we're just
6 going to the constituents that we don't have
7 information on.

8 Dr. Farone?

9 DR. FARONE: Well, the list that many of
10 these are on gives you a range of numbers that were
11 determined in cigarette smoke or some other place. In
12 other words, for acetamide, for example, it says the
13 range was 2.2 to 111 micrograms.

14 So to me, obviously, a method exists that
15 allows you to get a quantitative number. Now, whether
16 that meets any of the criteria, that's a different
17 issue. But I think that for anything on this list
18 where IARC reports a number, we can assume that a
19 method exists. Otherwise, they couldn't have reported
20 the number.

21 DR. HECHT: Actually, the list you're
22 talking about is mine.

1 DR. FARONE: Yes.

2 DR. HECHT: So when there's a reference
3 given that's in parentheses, like reference 30 for
4 acetamide, that means it's been recently determined.
5 But if there's no reference in parentheses, then
6 either it says "present," which means there's no
7 number available, or the data come from all their
8 literature. They're just quoted in the IARC
9 monographs.

10 So where there's a reference, there's
11 something recent. So we can say there's a method.

12 DR. FARONE: Right, right. So there is a
13 method and where there's a question, like the ones
14 where it just says "present" or whatever, then we
15 might want to discuss it a little bit further is my
16 point.

17 DR. HATSUKAMI: So it appears that based
18 upon the list, at least acetamide does have -- it has
19 a reference, so there is a method; so if you want to
20 put yes to that.

21 Acrylamide, same thing, that there is a
22 reference. Aflatoxin, I would imagine there probably

1 is, yes.

2 DR. FARONE: Well, there's an amino assay
3 method that's used on grain all over the place. So
4 there is a method. Whether that's adequate for
5 tobacco is another question.

6 DR. HATSUKAMI: Dr. Hecht, do you want to
7 comment or you don't know?

8 DR. HECHT: I haven't seen anything. I've
9 heard some comments from Mirjana and Dr. Heck. I've
10 never seen anything.

11 DR. HATSUKAMI: So there is no method that
12 we know of at this point in time; is that right?

13 DR. FARONE: Well, there is a method that's
14 used for grain and for grasses and everything else.
15 And so there is a method, because if you run an
16 ethanol plant on corn, every load of corn that comes
17 in, you're required by law to measure aflatoxin. So
18 there's a method.

19 Now, the question is, do you get into
20 trouble with that method when you try to apply it to
21 tobacco, and I don't know the answer to that.

22 DR. HATSUKAMI: Dr. Djordjevic?

1 DR. DJORDJEVIC: But there is a report that
2 aflatoxin is present in flue-cured tobacco. So it was
3 determined. So there must be some method.

4 DR. HATSUKAMI: Okay.

5 DR. HECK: There are reports I literature of
6 aspergillus flavus, the mold that produces, in some
7 conditions, aflatoxin that will grow in improperly
8 stored or improperly wet tobacco, spoiled tobacco.

9 The methods that are commercially available,
10 everything from kits to certified reagents for food
11 testing from milk, grains, things we've mentioned.
12 There is not or at least was not a couple of years ago
13 one available and certified and approved for a tobacco
14 matrix.

15 But I think one-off experiments have been
16 done with something as simple as fluorescence to
17 determine that in some -- the literature I'm recalling
18 is from, I think, Egyptian tobacco products that were
19 probably not manufactured or stored correctly, that
20 aflatoxin or apparent aflatoxin was detectable by
21 fluorescence. But how generally applicable those
22 methods may be, I don't know.

1 DR. HATSUKAMI: Okay. So what's the
2 committee's favor? Should we put yes or should we put
3 unknown? Okay. We'll put unknown.

4 Ammonia salts, we deferred on that, but I
5 think it'll be important to indicate whether there's -
6 - yes? Unknown? I can't tell. Yes, okay. All
7 right, yes.

8 Ortho-anisidine, yes. A-alpha-C, yes.
9 That's right. Some of these are already listed on
10 that.

11 So benz[a]anthracene, it appears that we do
12 have a method.

13 DR. HECHT: They're all --

14 DR. HATSUKAMI: They're all -- all of them
15 have methods. Okay. Benzene has a method, as well,
16 yes. Benzo[b]furan? No. We do not have a method for
17 benzo[b]furan? Unknown?

18 DR. LAUTERBACH: I'm sorry. Which one are
19 we on?

20 DR. HATSUKAMI: Benzo[b]furan. I guess it's
21 unknown. Beryllium, method? Yes. Okay.

22 Caffeic acid, yes. Chrysene, yes. Cobalt,

1 yes.

2 DR. HECHT: So this is the one that John was
3 mentioning. Why is coumarin on there?

4 DR. LAUTERBACH: Well, Dr. Hecht, as you may
5 remember, coumarin was used until about 1980 in the
6 U.S. tobacco industry, maybe a little bit later than
7 that for pipe tobacco. So, yes, there are some
8 methods out there.

9 DR. HECHT: I'm just asking why is coumarin
10 on the list at all.

11 DR. HUSTEN: Because it appeared initially
12 that that's what the committee said, but that's why we
13 put down it was Group 3, because we weren't clear
14 whether you wanted those on the list or not.

15 DR. HECHT: Because this is from tobacco,
16 not smoke. So we never really discussed it. Should
17 we use the same criteria?

18 DR. HATSUKAMI: We could use the same
19 criteria, if that's what the committee feels is
20 important to do. So based upon the criteria, coumarin
21 should not be on the list. All right. Everybody
22 agree with that? Okay. Let's take that off the list.

1 DR. WATSON: Dorothy?

2 DR. HATSUKAMI: I'm sorry.

3 Dr. Watson?

4 DR. WATSON: Methods do exist for coumarin.

5 We do see coumarin in various international products.

6 But if there's no toxicological reason for including
7 that, that's one thing.

8 I'm not a toxicologist, but it's a banned
9 substance. Are you guys okay with just dropping
10 coumarin? We can measure it, and its use was
11 discontinued. There must have been a reason why it
12 was discontinued.

13 DR. HATSUKAMI: Dr. O'Connor?

14 DR. O'CONNOR: I was going to add that it's
15 one of those constituents where it's banned by the FDA
16 for use in food. And if it's not currently used by
17 the U.S. tobacco industry, it may be an important
18 constituent to look at for imported products, like Dr.
19 Watson said.

20 DR. HATSUKAMI: Dr. Farone?

21 DR. FARONE: If it's banned for use in food,
22 that's why it didn't show up on the smoke, because

1 that issue was addressed earlier. The question is on
2 putting things in your mouth for ingestion. If it was
3 normally banned for use in foods, is it then,
4 therefore, allowable for use on smokeless tobacco?

5 So I think that's how it ended up here.
6 Whether we should keep it there or not, I don't know.

7 DR. HATSUKAMI: Dr. Lauterbach?

8 DR. LAUTERBACH: Excuse me. Dr. Farone,
9 could you please clarify what you just said there?
10 You said something about banned in foods. Does that
11 mean you're saying it's okay for smokeless or banned
12 in smokeless, too?

13 DR. FARONE: I didn't render an opinion. I
14 said the reason why it got on the list from our
15 previous discussion was because of the questionable
16 use of it in food. And that means things you put in
17 your mouth, which means the potential for ingestion.

18 So if you add it to smokeless tobacco, could
19 you potentially ingest it as you would a flavor in a
20 food? I think the answer to that is yes. I'm not
21 sure that's a sufficient reason to keep it on the
22 list. That's the question that I was raising.

1 DR. HECHT: I'd say keep it on.

2 DR. HATSUKAMI: Keep it on.

3 DR. HECHT: Yes.

4 DR. HATSUKAMI: All right. So we're going
5 to keep it on.

6 Is that of concern to people? Dr. Heck?

7 DR. HECK: Just a comment. Coumarin is
8 banned, as such, I think since 1958, as an ingredient
9 added to food in the U.S., but coumarin does occur
10 widely in the plant kingdom and it occurs in a lot of
11 spices, botanicals and other things that are -- it's
12 like an active principal in the European regulation,
13 where its addition, as such, is prohibited, but a
14 tolerance is set for its natural occurrence in a
15 variety of foods.

16 DR. HATSUKAMI: I think that maybe what we
17 should do is include it. If there's any objections to
18 that, then -- no. Okay. Let's go on.

19 All these other constituents, it appears
20 that there are methods, because you have references on
21 them.

22 DR. HECHT: No.

1 DR. HATSUKAMI: No?

2 DR. HECHT: Cyclopenta pyrene, there's a
3 method.

4 DR. HATSUKAMI: Yes.

5 DR. HECHT: But I think for the
6 dibenzacridines, that's questionable.
7 Dibenzanthracene, there's a method. But
8 dibenzcarbazole is questionable.

9 DR. HATSUKAMI: How about the pyrenes?

10 DR. HECHT: They're all there.

11 DR. HATSUKAMI: Yes. Okay. How about the
12 2,6-dimethylaniline? Yes? Okay. Ethyl carbamate,
13 no?

14 DR. HECHT: Question mark.

15 DR. HATSUKAMI: A question mark? Okay. Put
16 a question mark. All right.

17 Ethylbenzene? Don't know?

18 Dr. Watson?

19 DR. WATSON: There are methods.

20 DR. HATSUKAMI: There are methods. Okay.
21 Yes.

22 Ethylene oxide, methods? No. Okay.

1 Furan, methods? Yes.
2 Glu-P-1, yes. Okay. Glu-P-2, yes.
3 Hydrazine?
4 DR. HECHT: Question mark.
5 DR. HATSUKAMI: Question mark. Okay.
6 Indenopyrene?
7 Dr. Hecht, is there a method of analysis for
8 indenopyrene?
9 DR. HECHT: Yes.
10 DR. HATSUKAMI: Yes. Okay. How about IQ?
11 DR. HECHT: IQ, yes.
12 DR. HATSUKAMI: Yes. Okay. All right. 5-
13 methylchrysene, are there methods of analysis for
14 that?
15 DR. HECHT: Yes.
16 DR. HATSUKAMI: Yes. Okay. And then>NNL?
17 DR. HECHT: Yes.
18 DR. HATSUKAMI: Naphthalene?
19 DR. HECHT: Yes.
20 DR. HATSUKAMI: Nitrate? Nitrite, I'm
21 sorry. Nitrite. Yes, there is.
22 Nitrobenzene, yes. Okay.

1 Nitromethane, yes. Okay.

2 DR. HECHT: I don't know about nitromethane.

3 DR. HATSUKAMI: Okay. Anybody?

4 DR. HECHT: I don't know.

5 DR. HATSUKAMI: How about 2-nitropropane?

6 You said I don't know for that? No or I don't know?

7 DR. HECHT: No.

8 DR. HATSUKAMI: No. Okay.

9 NDELA, yes.

10 Nitrosodiethylamine, yes.

11 Nitrosoethylmethylaniline?

12 DR. HECHT: Yes. Yes for all the nitroso

13 compounds.

14 DR. HATSUKAMI: Okay. Great. Thank you.

15 Thank you, Dr. Hecht.

16 DR. HECHT: Wait a minute.

17 Nitrososarcosine, yes.

18 DR. HATSUKAMI: Excuse me. Dr. Watson?

19 DR. WATSON: Sorry. It takes me too long to

20 search here. There are methods from Hoffmann for

21 nitromethane, 2-nitropropane, and nitrobenzene.

22 DR. HATSUKAMI: Okay.

1 DR. HECHT: Okay. Those are kind of old and
2 they haven't been repeated.

3 DR. WATSON: That's true. They're from
4 1968.

5 DR. HATSUKAMI: So what should we do; say
6 yes, because they have been, or remain a question
7 mark?

8 Dr. Watson? Dr. Farone?

9 DR. FARONE: Well, if we're not comfortable
10 as a group, I think we say question mark. I think
11 that we're here to sort of make that judgment for FDA.

12 DR. HATSUKAMI: Okay. So we leave the
13 question mark. How about the nitropropane, should we
14 have a question mark on that? Yes. Why don't we
15 change the no to question mark?

16 What was the other constituent, Dr. Watson?
17 I missed that.

18 DR. WATSON: I think we said yes -- I may
19 have gotten lost -- the nitrobenzene. There's a
20 reference at least from 1970.

21 DR. HATSUKAMI: Okay. How about the Ph1P?
22 Yes. Okay.

1 Polonium, yes.

2 Propionaldehyde, yes. I'm sorry.

3 Propylene oxide, no. Is it a no or a
4 question mark? It's a no, right?

5 DR. HECHT: I think it has to be a question
6 mark, because if it's on the list, it's been
7 identified at some point. The question is, is there
8 really a quantitative method.

9 DR. HATSUKAMI: Okay. 2-toluidine.

10 Yes, Dr. Watson?

11 DR. WATSON: Sorry. I'm always a half-step
12 behind here. Was the last one propylene oxide?

13 DR. HATSUKAMI: Yes.

14 DR. WATSON: There is a Labstat method for
15 that.

16 DR. HATSUKAMI: Okay. So put yes.

17 DR. O'CONNOR: I was just going to say
18 there's also a published one in the *Journal of*
19 *Chromatographic Science* for propylene oxide.

20 DR. HATSUKAMI: Great. Thanks. 2-
21 toluidine.

22 DR. HECHT: Yes.

1 DR. HATSUKAMI: Yes. Okay. Trp-P-1, yes.

2 Trp-P-2, yes. All right.

3 Uranium-235, yes.

4 Vinyl acetate. Yes? Is there a method for
5 that? Unknown?

6 DR. O'CONNOR: I found one from Diekmann, et
7 al, 2002, *Journal of Chromatographic Science*.

8 DR. HATSUKAMI: Okay. Great. Yes.

9 Vinyl chloride, yes. Okay. All right. We
10 have our list and we have an indication of whether
11 there is an analytic methods.

12 Before we move on to -- yes, Dr. Burns?

13 DR. BURNS: It occurred to me that it might
14 be helpful if we asked for some information before the
15 next meeting. And if we could ask the CDC lab and Dr.
16 Rickert and Dr. Higby to produce for us, from the list
17 that we've just gone through, a statement about
18 whether their lab, at this moment in time, has a
19 procedure by which these constituents can be measured,
20 that is, on a commercial basis; and, then, secondly,
21 to format that list by test.

22 That is, if you're going to do one test and

1 generate 5, 6, 10 PAHs or nitrosamines from it, that
2 you would list the test and then the fact that you can
3 make all of these measurements in your laboratory at
4 this moment in time, quantitatively, from that
5 particular test.

6 That would give us the answer to the
7 questions of the number of tests that would be
8 required, which is different than the number of
9 constituents that we're recommending measurements for.
10 And secondly, it would give us some reassurance that
11 existing laboratories that would normally be relied on
12 to generate this kind of information for a
13 governmental entity can produce quantitative
14 information on these individual metrics, and will also
15 identify for us the gaps.

16 DR. HATSUKAMI: I think that's an excellent
17 idea.

18 DR. LAUTERBACH: I'd like to add to
19 Dr. Burns' request there, saying, also, the labs
20 should provide standard figures of merit in terms of
21 repeatability, anything they know on reproducibility
22 between labs, and anything in terms of recovery,

1 whatever, and whether it's smoked under ISO or smoked
2 under Health Canada conditions, or whether it's on
3 tobacco such as smokeless.

4 DR. BURNS: Well, I'm reluctant to place too
5 great a burden on these folks, but certainly we should
6 know whether or not the laboratory can make the
7 measurement, and I would expect that perhaps we ought
8 to know it under which conditions; that is, Health
9 Canada versus the FTC method.

10 I think the issues of cross-laboratory
11 standardization and the rest are somewhat beyond the
12 task of this particular committee and I'm reluctant to
13 get into trying to establish a discussion about
14 whether a 3-lab cross-validation is better or worse
15 than 7-lab or a 10-lab.

16 Those are issues that certainly, as the FDA
17 comes to the decision about how they will write
18 regulations, they would have to work through. But I'm
19 reluctant to have us get into discussions that are
20 beyond the charge that we have been given at this
21 point in time.

22 DR. LAUTERBACH: Well, I tend to disagree

1 with you, Dr. Burns, because there's a feeling, I
2 gather, around, with the comments of this committee,
3 that these methods are very finely tuned and can
4 differentiate between cigarettes that only differ by a
5 small amount, and that's not been my experience with
6 them.

7 In fact, generally, unless you have a
8 difference of more than 20 percent on seven or eight
9 replicates, you don't have a difference.

10 DR. BURNS: I don't recall a discussion of
11 the magnitude of the differences that would be
12 required to distinguish between brands at this
13 meeting. I don't recognize that that was the task
14 that we were assigned to define what magnitude of
15 difference would be significant between brands.

16 We were, as I understand it, asked to define
17 whether the substances were toxic, whether they were
18 present in tobacco and in tobacco smoke, and whether
19 there are reliable analytic methods that can produce a
20 quantitative estimate for those numbers.

21 I understand that there's a variety of other
22 issues that will come to play as regulations need to

1 be written, but I would put those issues beyond the
2 scope of this particular committee.

3 DR. HATSUKAMI: We're going to actually be
4 talking about some of those parameters in our
5 discussions once we get off the list issues. So it
6 will be brought up.

7 What I want to do is I want to -- before we
8 get into some of the issues regarding the scientific
9 parameters that we need to consider in choosing
10 methods, I want to make sure that we feel comfortable
11 with what we have now before we proceed onto the next
12 topic.

13 Any concerns from anybody regarding the list
14 and what we've established so far before proceeding
15 on?

16 It is also my understanding that in the next
17 meeting, we would have some information on the
18 criteria by which we chose the constituents. So that
19 if we could have that available to us, we can review
20 that, as well.

21 If there's no further concerns, then I think
22 we have our preliminary list and we'll proceed on to

1 the next topic. We were asked to -- actually, I just
2 got three additional issues that the FDA wanted this
3 committee to consider.

4 The first issue was, again, just to
5 reiterate, what scientific parameters need to be
6 considered in choosing methods to be used. The second
7 issue is scientific recommendations on sampling; that
8 is, the frequency of sampling, should it be once a
9 year, twice a year, based on information about the
10 variability of the product, as well as the smoking
11 regimen or regimens.

12 The third question that they wanted us to
13 entertain is your scientific recommendation on how
14 values should be normalized, by product unit, by
15 volume, or by nicotine.

16 So why don't we go ahead and start with the
17 first question, which is what scientific parameters
18 need to be considered in choosing methods to be used,
19 methods of analysis. And I think we were starting to
20 have discussions on that particular topic.

21 Yes, Dr. Farone?

22 DR. FARONE: Well, this might be worth

1 mentioning, and I don't know if Dr. Jinot would like
2 to comment, also. But normally, if you look at
3 acceptance criteria for methods that have been used
4 for regulatory things before, the one that I'm most
5 familiar with is the one that says you look at the
6 sensitivity of the instrument and if what you're
7 looking for is less than 20 times that, that's a low
8 level analyte; then you have where it's more than 20
9 times the detection limit as being a high level
10 analyte.

11 If I recall the acceptance limits, they're
12 different like for volatile organics and for metals,
13 and it depends on the test. But they run, for the
14 high level analytes, plus or minus 20 percent on down
15 and for low level analytes, plus or minus 50 percent.

16 In other words, what I'm saying is there are
17 criteria that have been developed for all kinds -- for
18 air analyses, water analyses of this type that have
19 been used for decades, and maybe that provides us some
20 guidance for how to do it in this particular case,
21 because I don't see much difference between this and
22 looking for, say, TCE in water, as far as the

1 acceptable analytical differences go.

2 There's a big difference in the methods, but
3 just the parameter of how -- what's an acceptable
4 analytical method and what isn't.

5 DR. HATSUKAMI: Any comment?

6 [No response.]

7 DR. HATSUKAMI: When these questions are
8 asked, I think that it will be really critical for the
9 committee to think about information that we will need
10 at the next meeting in order to address these
11 questions that they're asking us.

12 DR. FARONE: Good. Maybe we could look at
13 some of the other, like, EPA and FDA and other areas
14 for foods and look at what the acceptable criteria
15 area for variability, because everybody knows they
16 vary and it's been done with all of these other
17 methods.

18 So like we have with IARC criteria and the
19 rest of it, rather than reinvent the wheel, why don't
20 we just see what's been done?

21 DR. HATSUKAMI: Okay.

22 Yes, Dr. Burns?

1 DR. BURNS: I think you can bifurcate that
2 into two areas, one where you have a lot of
3 information and one where you don't have much
4 information. A lot of folks have had to approach the
5 question of if you're going to use a metric as a
6 regulatory standard, how do you go about doing that,
7 and I would expect that that's fairly well worked out
8 in terms of what's required, the kind of thing that
9 Bill just talked about.

10 I think as we have done with other
11 international or other reviews, we can simply adopt
12 that same process. The issue that comes up is whether
13 the variability of the method is dramatically smaller
14 than the variability of the same measure across the
15 various brands on the market, because quite obviously,
16 as Dr. Lauterbach has pointed out, you can't have
17 something that you're measuring if you can't tell the
18 difference between products or at least it doesn't
19 make much sense to measure it.

20 I would suggest, at this point in time, that
21 we have a quite incomplete dataset to understand that
22 for the U.S. tobacco market as it's currently

1 constituted.

2 There are datasets for some of these
3 constituents that can be used to inform us, but they
4 are from international Philip Morris brands; they are
5 from the Massachusetts benchmark study.

6 There's been some recent publication, I
7 believe, from Philip Morris, although I didn't look at
8 the detail of their smoke chemistry data, but I
9 thought they presented it recently in an effort to do
10 some kind of market benchmarking process. And, of
11 course, there's the Canadian and Australian data that
12 can inform us.

13 But the reality is the only way you're going
14 to know what the variability on the U.S. market is is
15 to know what the variability on the U.S. market is and
16 until we have that information, you're operating from
17 extrapolation or conjecture about what that data would
18 show.

19 So I think the reality is you're going to
20 come down to, at least in a first instance, trying to
21 make the measurement and see what the variability is
22 rather than dismissing things because variability in

1 other datasets has been small.

2 DR. HATSUKAMI: So I'm just trying to get my
3 hands around what you're saying. In terms of the
4 scientific parameters that we need to consider, then
5 we need to consider the variability of the method,
6 because if there's a great deal of variability in the
7 method, then we wouldn't be able to detect variability
8 in the brand. So that is one parameter that we should
9 consider.

10 DR. BURNS: Yes. To put it in terms that my
11 simple mind can get around, you have a reproducibility
12 of the measurement for a given brand in a given
13 laboratory. And I understand that you need to do it
14 across laboratories and all the rest. I'm just
15 dealing with it in a way that I can understand
16 conceptually at the moment.

17 Then you have a coefficient of variation of
18 the mean value of that measurement with three
19 replicates or seven replicates, or whatever number you
20 specify, across the brands. And quite obviously, for
21 the measure to be of value, the coefficient of
22 variation across brands has to be some multiple of the

1 coefficient of replicate measurements -- the
2 coefficient of variation of the replicate
3 measurements. And that's what I'm referring to.

4 We actually did that calculation for many of
5 the elements that -- we did it for Massachusetts and w
6 also did it for Canada and for -- I don't think we did
7 it for Australia, but we did it for the Canadian data
8 and we did it for the Philip Morris international
9 data. For many of the constituents, that

10 ratio was well above two to three. For some of them,
11 it's below that. So that, I think, is a piece of
12 information that will inform the FDA about what
13 decisions they may want to make about reporting
14 requirements, but it doesn't -- other than perhaps
15 presenting it, it doesn't influence our decisions,
16 because we're not asked what should be reported.
17 We're simply asked to define toxicity and whether
18 methods are available to make the measurement.

19 But it does suggest that it may be useful
20 for us to present to the FDA the information that does
21 exist on variation across brands in relation to the
22 variation of the replicate measurement.

1 DR. HATSUKAMI: Yes, Dr. Lauterbach?

2 DR. LAUTERBACH: To follow-up with Dr.

3 Burns, for example, the Mary Ellen Counts study, that
4 was product taken in 2000-2001 from the Philip Morris
5 factories. It was not a market pickup, such as it
6 used to be for the FTC sampling.

7 It's one thing with the big manufacturers
8 and their long runs. With the small manufacturers and
9 very short runs, how we're going to sample that, how
10 you're going to sample some of the smokeless products,
11 I think does present some issues almost as big as some
12 of the method issues.

13 DR. HATSUKAMI: Dr. Watson, do you have
14 anything to add to this particular question, since you
15 presented some of the information?

16 DR. WATSON: Basically, I agree with
17 everyone. There are some limited data that have been
18 published looking at sort of variabilities, inter-
19 laboratory comparisons.

20 Presumably, these, again, have been done for
21 other areas, pharmaceuticals. Tobacco is unique in
22 terms of the composition and the variation and the

1 seasonal variations. It's not a pharmaceutical
2 product, obviously, so the variation would be expected
3 to be bigger.

4 There have been a few publications in the
5 last decade that sort of address this, which we can
6 use for some guidance. But it gets tricky very
7 quickly because, for instance, if you were to adopt
8 the ISO smoking regimen, where the filter ventilation
9 holes are open, and you're diluting the mainstream
10 smoke, obviously, you'll have a much bigger variation
11 in the product delivery than you would, say, if you
12 tape the holes shut.

13 So not to go round and round in circles
14 here, but it depends a little bit on what sort of
15 measurement you want to make. And to my knowledge,
16 and correct me if I'm wrong here, there haven't been
17 many inter-laboratory comparisons using the so-called
18 Canadian intense method.

19 I mean, there are some undergoing right now
20 with the TobLab Network, and maybe we can see if we
21 can tap into some of their findings to see sort of
22 what are expected ranges. But again, we have to take

1 it with a grain of salt, because that may vary
2 tremendously by constituent. So we can't just take a
3 one-size-fits-all approach here.

4 Getting back to the small manufactures, I
5 mean, this may sound very cold-hearted, but they don't
6 have much market share. And so I don't want to ignore
7 the harm that those products cause, but, basically, if
8 we could take a sampling of the brands that have the
9 majority of the market share, that really is what is
10 impacting public health, and that's really ultimately
11 what we're getting after here.

12 DR. HATSUKAMI: Dr. Farone?

13 DR. FARONE: Yes. There have been studies
14 done by companies on their own products using their
15 method and then a different company would do a
16 different study using their methods on products. Like
17 Philip Morris would look at RJR's products and RJR
18 would look at Philip Morris'.

19 A lot of these have been -- they're not
20 published, but they're kind of available. And that
21 would give us -- if we could compile some of the
22 information from that -- an idea of the variability,

1 both the way it turns up in a given test across
2 products and when different people did it.

3 I mean, if everybody is getting the same --
4 I'll make it simple. If everybody is getting the same
5 difference in numbers and they're using somewhat
6 different methods and they're looking at their own
7 products and somebody else's, and when they measure,
8 say, NNK, they always see 2-to-1 in this product
9 versus another, no matter how they were -- that would
10 give you a lot of confidence that that particular
11 analyte is fine, because you can get at it from
12 different methods and the laboratory variation was
13 giving you approximately the same result.

14 So maybe that's a literature something that
15 could be done to kind of compile those kinds of
16 comparisons, where it's available, where people have
17 published it.

18 DR. HATSUKAMI: Good point.

19 Any additional comments? Yes, Dr. Heck?

20 DR. HECK: Just to follow-up Dr. Farone's
21 comment. Comparative brand analysis is indeed done,
22 has always been done as a normal part of a competitive

1 consumer product marketplace.

2 I would caution, though, that oftentimes,
3 such analyses are indeed done by house methods of
4 specific methods or methods that are specific to an
5 individual company, and there's some broad
6 comparability, I think, in some instances, but we very
7 quickly run into -- and we've seen instances of this
8 in the published literature -- the incompatibility of
9 the findings from one such house method to another
10 does really intrude on our ability to collate and
11 consider together, side-by-side, some of those
12 analyses.

13 DR. FARONE: May I respond?

14 DR. HATSUKAMI: Yes.

15 DR. FARONE: To Dr. Hecht's point, I was
16 thinking the other way around. It's where there is no
17 incompatibility. You learn a lot more, whether
18 everybody is getting the same result.

19 So I agree with you that there are instances
20 where two companies will do it and they'll get a
21 different result. And I'll say, "Well, okay, that's
22 something where we may have to think more about it."

1 But if they are using different house
2 methods and if those methods are published or are very
3 well known or are similar to ones that have been used,
4 that have been published and caressed, or some other
5 place. And what we find is they're getting roughly the
6 same numbers that would give us a lot of confidence
7 that that's a good place to say, "Okay, this is done
8 and ready to go."

9 DR. HECK: As long as that's done judiciously
10 and conservatively, because I can think of instances
11 where numbers have been plucked and presented in the
12 literature and quite erroneous conclusions were drawn
13 from perhaps a well intentioned effort to do just
14 that.

15 DR. HATSUKAMI: Dr. Watson?

16 DR. WATSON: I'd like to sort of follow-up
17 on that just a little bit. I think that's a point
18 well taken. So I think many of these sort of internal
19 studies, at least my reading of these, are often
20 looking -- they're looking at relative differences.
21 They're not looking at absolute quantities.

22 So they're looking at is effect bigger or by

1 doing this change or that change, how does that affect
2 the chemistry on a percent basis. And so one has to
3 be very careful, looking at these documents, to make
4 sure that we are sort of comparing things on a similar
5 basis.

6 DR. HATSUKAMI: Any other comments?

7 [No response.]

8 DR. HATSUKAMI: It sounds like what we need
9 is some additional information for the next meeting to
10 more thoroughly address this particular question.

11 The second question that they wanted us to
12 address is your scientific recommendations on
13 sampling; that is, the number of times of sampling,
14 based on information about variability of product,
15 which is what we were talking about, as well smoking
16 regimen or regimens.

17 Maybe we can have a preliminary discussion
18 on that right now.

19 Dr. Burns?

20 DR. BURNS: Well, I think the answer to the
21 frequency of sampling is going to be it depends and
22 you're not going to know the answer to that until you

1 have actual evidence for the U.S. market.

2 I think, at this point in time, we can feel
3 confident we don't need to sample on a quarterly basis
4 and generate numbers every quarter, that a longer
5 interval than that is appropriate.

6 But until you have a couple of measurements
7 at different intervals, you're not going to have any
8 kind of reasonable measure of how much variability
9 there is between brands for the U.S. market.

10 While Canada almost certainly has the data
11 for more than one year for the same brands, it's not
12 readily accessible and it might be useful to formally
13 see whether there isn't a way to get that information
14 from Canada, because they have put out on the Web the
15 data for 2004.

16 My assumption is, and Bill would know, they
17 generate that data every year. Is that correct? So
18 it would indeed be possible then to get some estimate
19 of what another country's market has in terms of
20 variability in the same brands over time that might
21 inform that decision.

22 But the truth is that until you know what

1 your variability is in the U.S. market, you're not
2 going to know what the variability is in the U.S.
3 market.

4 On the second issue of smoking regimens, I
5 think it is very clear from the work we did with WHO
6 that not only does the amount of smoke change with the
7 smoking regimen, but the ranking of the constituents
8 one to another, the ranking of the brands by
9 constituent also change. Most constituents go up with
10 the Canadian method, but a couple of them go down.

11 What we also point out is for several of the
12 constituents, as Cliff has pointed out, the mass of
13 smoke that you get for a given test with the FTC
14 method is small enough that you get a much larger
15 variability in your measurements, and that getting a
16 larger mass of smoke, as you do with the Canadian
17 intense method, simply gives you more material from
18 which to derive a better estimate.

19 Given that variability and given the reality
20 that the purpose of doing this is to look at the
21 performance characteristics of the product, I think it
22 is reasonable to expect that at least two methods

1 would be required. And at this point in time, the two
2 that have the greatest international following, it's
3 perhaps the best term for it, are the FTC method/ISO
4 method and the Canadian intense.

5 DR. HATSUKAMI: Any discussion? Dr. Farone?

6 DR. FARONE: Yes. Well, I think we started
7 this meeting by having the list of what Australia and
8 New Zealand and what other people had done on
9 constituents. And I think maybe for the next meeting,
10 although a lot of us know some of the bits and have
11 been involved in it ongoing, to have that formalized
12 as to what people have been doing in different places,
13 so that we don't have to reinvent the wheel, if it
14 turns out that any subset or group that is acceptable
15 to recommend to FDA, that would seem to be another --
16 well, I don't want to use the word easy, but it would
17 be another direction that we could take to try to come
18 to a discussion in a more refined way.

19 So I think that may be something we'd like
20 to have for the next meeting is a list of what are the
21 decisions that Canada made and Australia and Brazil
22 and WHO and what they recommended. We all know pieces

1 of that. To have it in one place might be useful.

2 DR. HATSUKAMI: That's an excellent idea.

3 Rich, do you have any comments?

4 DR. O'CONNOR: I would agree with Dr. Burns'
5 assessment that you'd probably want at least two
6 methods. The ISO and Canadian intense are the ones
7 that have been used. There are data on them that we
8 can examine variability and repeatability.

9 So they would seem to be reasonable choices
10 to make or recommendations to make, but ultimately
11 it's not our decision to make or pick a method or
12 dictate one.

13 DR. HATSUKAMI: Any other comments?

14 Dr. Heck?

15 DR. HECK: I know we're getting -- looking
16 ahead, I think that's positive, looking forward
17 towards the method or methods to be applied, but I
18 would remind the committee, just for thought, the ISO
19 method is an internationally accepted standard, not
20 exactly equivalent to FTC, but very, very, very
21 similar, for which we have about a 50-year track
22 record of the performance of commercial products.

1 I guess, as I understand, the original
2 rationale for the imposition of the Canadian intense
3 method was to reflect a maximum possible conceivable
4 way that an exceptional smoker could conceivably
5 intensely smoke a cigarette with 100 percent vent
6 blocking.

7 The way people smoke cigarettes, I think, is
8 a question of interest, but I think my own view is
9 that machine analytical smoking has value for the
10 purposes of comparing cigarettes by the best, most
11 standardized way we can do that. And the question of
12 how people may smoke cigarettes is a perfectly valid
13 one, but best answered by other methods outside of
14 machine smoking, including biomarkers and, indeed, the
15 yield-to-use studies that the CDC and others have
16 explored recently.

17 So I think, in my view, the pursuit of a
18 dual method kind of perpetuates this conception, or
19 maybe misconception, we've had that any machine method
20 or combination method can really reflect a spectrum of
21 the way people smoke.

22 If we want to know how people smoke, let's

1 go to people for the purposes of our best ability to,
2 in a valid or close to valid way, compare cigarettes.
3 Let's stick to the most established standard method,
4 and I would recommend that be the ISO method.

5 DR. HATSUKAMI: Jack?

6 DR. HENNINGFIELD: The ISO method has been
7 used for decades, but the WHO has lodged a complaint -
8 - I'm not sure what the formal term is -- but to ISO
9 that its method essentially was misleading and
10 generally underestimated deliveries.

11 The Federal Trade Commission, as you know,
12 in 2007, also walked away with very strong language
13 and with language including, I think, words to the
14 effect that it has been used to deceive the American
15 public. So I think that that's not where we should
16 be going.

17 DR. HATSUKAMI: Dr. Burns?

18 DR. BURNS: I wanted to interject something.
19 The purpose of using two methods is not to mimic human
20 smoking behavior. The purpose of the two methods is
21 that the product performs differently under different
22 conditions and, therefore, examining it under only one

1 condition gives a less complete picture than examining
2 it under at least two conditions.

3 In a hypothetical ideal world, one might
4 want to examine it under an envelope of conditions,
5 but that clearly doesn't exist. And so it is
6 important to examine what happens when the product is
7 used under different conditions, even though neither
8 of those conditions match what happens with the normal
9 human smoking behavior.

10 Secondly, I believe, and you can correct me
11 if you have more current data, but I believe that ISO
12 is currently undertaking the process of standardizing,
13 in its own format of standardization, the Canadian
14 intense method.

15 DR. HATSUKAMI: Dr. Heck?

16 DR. HECK: Yes. There are indeed efforts
17 going on right now to develop a method that -- a more
18 intense method or a way that reflects perhaps
19 something other than an analytical standards method,
20 such as ISO, that may reflect the way some persons do
21 smoke.

22 But I just feel, at some point, there's

1 diminishing returns from a dual process here that has
2 the potential of really taxing world capacity to look
3 at as broad a spectrum of constituents as we may wish.

4 So I just want us to think about these other
5 factors involved in the imposition or the
6 consideration of a dual regime. And as Dr. Burns
7 said, a triple or quadruple regime would definitely be
8 more informative, but there's a point at which we can
9 only gather so much data or produce so much data and
10 interpret so much data.

11 I think there's something to be said for
12 adherence to what has emerged as a consistent
13 analytical standard internationally, with the
14 questions of how people may smoke and the extreme, a
15 worthy one, but best answered by other methods.

16 DR. HATSUKAMI: Dr. Farone?

17 DR. FARONE: Yes. We've been talking only
18 about smoking, and we don't have 60 years of
19 experience with a method like FTC for the smokeless
20 products. So I think there, it also behooves us to
21 look outside the country where people may have used
22 the products longer and there is a greater body of

1 literature on how they treated -- how they prepared
2 the samples.

3 I remember vividly yesterday Dr. Watson made
4 the point that he left blank on the top of his chart
5 the preparation of the sample to be considered later,
6 and I think that's a very, very important point for
7 smokeless.

8 So I think that's another reason to get
9 information from other places where it has been done
10 and to compare those. I mean, we're talking about two
11 different smoking regimes and the kind of data that it
12 gives us, and it's easy just to look and see what the
13 results have been from those two and how much
14 difference it made.

15 A lot of us know that, because we've looked
16 at some of the data, but I agree with Dr. Burns and I
17 think two ways of looking at it is going to be
18 essential so that we don't just get into the situation
19 of people changing the product to kind of meet the
20 test. I mean, we want to be able to get a fair
21 understanding of what the consumer is exposed to
22 without necessarily going through the entire range of

1 everybody smokes different, so I need to do this on
2 every individual.

3 We need some guidance on what will give us
4 the range that we expect 80, 90-some percentage of the
5 people to hit.

6 DR. HATSUKAMI: Any other additional
7 comments?

8 [No response.]

9 DR. HATSUKAMI: So what I'm hearing is that,
10 basically, what we need to do is have a little bit
11 more data to make our decision, maybe a more refined
12 discussion in terms of how these different sampling
13 methods might affect the constituent yields that we
14 observe; and, furthermore, what we need is greater
15 information in terms of potential methods maybe other
16 countries have used in looking at exposure to
17 smokeless -- methods to determine exposure to
18 constituents with smokeless tobacco.

19 Is that right? Is that what I'm --

20 DR. BURNS: Well, I think one of the things
21 that was suggested is certainly Canada and Brazil have
22 already established how they collect the cigarette

1 packs that they're going to go about making the
2 measurements on. That would be useful information to
3 have.

4 They've also established a frequency with
5 which they make that measurement. And as I said, if
6 we can get it, it would be useful to have the data on
7 the change within the same brand on the annual
8 frequency sampling in Canada. That would help define
9 the operational questions of if you're going to go out
10 and collect samples to make these measurements, how do
11 you actually go about doing that? Do you sample from
12 the four corners of the country? Do you sample four
13 seasons? Do you sample -- all of the operational
14 questions that are necessary to actually generate a
15 regulation as to how you would do it.

16 DR. HATSUKAMI: Okay. So maybe next
17 meeting, we can have those pieces of information.
18 Okay.

19 DR. DJORDJEVIC: Dorothy, I have a comment.

20 DR. HATSUKAMI: I'm sorry. Yes.

21 DR. DJORDJEVIC: In addition to Canada and
22 Brazil, the state of Massachusetts was collecting for

1 many years data on smokeless tobacco, and we have that
2 information about variability over the years. So that
3 would be also a useful presentation.

4 DR. HATSUKAMI: All right.

5 The third question is your scientific
6 recommendation on how value should be normalized; by
7 product unit, for example, per tin or per stick -- it
8 must be per cigarette; by volume, smoke volume, gram
9 of smokeless, for example; or, by nicotine or tar
10 content.

11 Any thoughts or discussion on that and
12 anything that we would like to be presented at the
13 next meeting?

14 Yes, Dr. Farone?

15 DR. FARONE: Yes. In other words, I don't
16 see why we're limited to one. I think one of the
17 presentations, I think it was Star yesterday made a
18 presentation which pointed out it's not too confusing
19 if you pick two. It's just like the calories and the
20 percentage of daily thing.

21 So as long as it's not too cluttered and
22 it's not too confusing, I don't think we necessarily

1 should limit our mind to one. I think there are some
2 of us who like to express things relative to nicotine,
3 because of the compensation issues and so on, but
4 there is some value in knowing about it per unit or
5 per units.

6 So I think both of those are useful and
7 might be useful to the public. So I don't think we
8 should limit ourselves to one.

9 DR. HATSUKAMI: Rich?

10 DR. O'CONNOR: Yes. I would tend to agree
11 with Dr. Farone. It depends on what specific use you
12 have for a particular data point and for some
13 purposes, it's perfectly fine to express things per
14 stick or per unit for smokeless; other times, it would
15 make more sense to look at things per unit volume or
16 per gram of nicotine.

17 It's not like it takes a lot of extra effort
18 to divide one number by another in data that you
19 already have.

20 DR. HATSUKAMI: Dr. Burns?

21 DR. BURNS: I would make a distinction here
22 between the format in which it should be reported and

1 the format that you might want to use for some other
2 purpose. And I would agree with Rich that the format
3 in which it should be reported is per stick, because
4 that allows you then to convert to almost any other
5 format.

6 Quite obviously, if you want to compare
7 across brands, you need to remove from the equation
8 the artificial distortion produced by the ventilation
9 in the filters. And so you need some normalization
10 process, either per gram of total smoke weight or gram
11 of tar or milligram of nicotine, et cetera, in order
12 to get a metric that reasonably allows you to compare
13 across products.

14 The issue of smoke volume has been
15 considered and largely dismissed as a metric simply
16 because the smoke volume incorporates all of the
17 uncertainties introduced by the ventilation of
18 filters, without adding any substantive advantage to
19 that calculation.

20 Again, with smokeless tobacco -- the reason
21 why I'm going on is that WHO had to struggle with all
22 of those same issues as it went through several

1 reports. And it makes sense to report the product for
2 smokeless with as much detail as you can with the
3 individual product, just as you do per stick with
4 cigarettes, and it allows you to normalize in multiple
5 different ways.

6 Probably the most valid normalization is per
7 gram of dry weight, although Dr. Higby has one that
8 he's fond of, as well, that may emerge as a valuable
9 tool. And the problem with wet weight is it is then
10 subject to the humidity of the environment in which
11 you purchased it or you condition the tobacco to a
12 fixed level of humidity, in which case, it no longer
13 reflects the value of wet weight, which is the way the
14 product is actually used.

15 So struggling through all of those different
16 potential ways to normalize it, the gram of dry weight
17 was the one that WHO thought was the most useful.

18 DR. HATSUKAMI: So for smokeless, you're
19 recommending looking at per gram of dry weight.

20 DR. BURNS: I'm recommending reporting it
21 with per gram of dry weight as one of the
22 characteristics that is present. And I think it

1 probably makes -- for smokeless, it probably makes
2 more sense to report all of your units per gram of dry
3 weight, although one could argue that if you report
4 units per dose, whatever the dose you want to choose,
5 as long as you then report the dry weight of that
6 dose, you could always convert it, just as you can
7 with tar and the constituents per stick.

8 DR. HATSUKAMI: Dr. Watson?

9 DR. WATSON: I sort of second that approach.
10 I like the idea of having a reported proportion size
11 or per dose, because that's, I think, something that
12 the consumer is familiar with. There may be some
13 variation, but you can do these conversions to convert
14 back and forth.

15 The other option is per gram of tobacco.
16 Per gram of dry tobacco is good, because as Dr. Burns
17 mentioned, that's a good way to sort of normalize the
18 data. And so if you're living in Florida or in
19 Arizona, you have the same sort of total content from
20 the tobacco and you're not worried about the relative
21 humidity changing the weight, because that can --
22 actually, the moisture content can vary considerably.

1 The other idea has been proposed several
2 times to normalize particularly things by tar or by
3 nicotine. And for nicotine, I think we should hold
4 off on that, because that's normally done because
5 that's seen as the main additive component in tobacco
6 smoke. And presumably people use the -- or tobacco
7 product. They pick a certain dose to achieve their
8 desired level of nicotine.

9 But as we're going to discuss, I guess, next
10 time, other components that may also be addictive, one
11 might want to look at sort of the sum of -- if you're
12 going to go down this road -- the sum of all addictive
13 compounds rather than just simply nicotine.

14 DR. BURNS: But, again, reporting per stick
15 allows all of those calculations to be done.

16 DR. WATSON: yes. But if you're going to
17 allow multiple things and you want to consider which
18 one is the best, I just want to put that little caveat
19 on the measurement solely based on nicotine content.

20 DR. BURNS: Right. The problem would be
21 that if we were to make the recommendations that you
22 report all of these metrics per milligram of nicotine,

1 it is then not possible to go back and do the other
2 kinds of conversions that you're talking about.

3 DR. HATSUKAMI: So just going back to what
4 you had said, Dr. Watson, you had mentioned that it
5 might be possible to even look at the amount of
6 constituents per portion size of smokeless tobacco.

7 How do you determine -- there's so much
8 variability in terms of portion size among --

9 DR. WATSON: I think that would have to be
10 defined by the manufacturer, but given a tin, you'd
11 have to have the weight, also, so you could do these
12 inter-conversions.

13 That might be something easier to guide the
14 consumer. I don't know how many portions are in a
15 typical tin. Obviously, one, on a cigarette, would
16 think one stick would be a serving size. And a tin
17 that has pouches, then obviously each pouch would be
18 considered a serving sizes. But if it's loose, then
19 what do you do?

20 There have been some topography results
21 published, sort of an average thing and you can sort
22 of get an average thing, but I think it might be

1 better to defer to the manufacturers and what they
2 consider a standard size; so you have information of
3 what the standard size is, plus how many are in the
4 tin so you can inter-convert back and forth.

5 DR. HATSUKAMI: Dr. Farone, and then
6 Dr. Henningfield.

7 DR. FARONE: This is a detail that we don't
8 really need to get into, but I just want to point out
9 that the use of dry weight is fraught with
10 difficulties, because of what you mean when you say
11 water in tobacco as compared to volatiles, as compared
12 to bound water.

13 There's a whole big literature discussion of
14 what tobacco dry weight really means. You put it in
15 an oven, you get off things that aren't water, and you
16 can still prove that there's some water left.

17 So it's okay as long as everybody is doing
18 the same thing, but I think this is one of the
19 situations where care needs to be exercised.

20 DR. HATSUKAMI: Dr. Henningfield?

21 DR. LAUTERBACH: Very well put, Dr. Farone.

22 DR. HENNINGFIELD: For smokeless tobacco

1 especially, the portion size issue is really an
2 important issue. A lot of us default to the Hatsukami
3 results. But there aren't a lot of data out there and
4 I think this is an area where I don't think we can
5 prescribe a specific portion method, but rather
6 recommend that FDA learn everything it has from its
7 successes and failures in food portion size and make
8 sure that communications to consumers are based on
9 realistic portion sizes, including perhaps total size
10 in the sales unit.

11 But, again, I think at this point, FDA has a
12 lot of experience with issues that include little bags
13 of potato chips, all kinds of things where people tend
14 to eat variably, and it's complicated. But they're
15 going to need real world consumer testing, what are
16 often referred to as actual use studies, and it's
17 going to be a moving target.

18 It's going to be one where it can, I think,
19 be assumed that the industry will be manipulating its
20 products and its packaging to beat the system.

21 DR. HATSUKAMI: Dr. O'Connor?

22 DR. O'CONNOR: Dr. Henningfield covered

1 largely what I was going to say, which is that we may
2 be straying a little bit and trying to get into issue
3 of portion size at this level rather than how the data
4 would be reported to FDA. And what FDA does with that
5 in terms of consumer communication is a completely
6 separate issue.

7 DR. HATSUKAMI: I don't think we've come to
8 any consensus in terms of the way that these products
9 should be -- the manner in which these products should
10 be reported. Certainly, there was some recommendation
11 that they should be reported per gram of dry weight,
12 but then there are some considerations that have to be
13 recognized.

14 DR. FARONE: Well, I'm just pointing out,
15 it's not that it means don't do it. It just means
16 that care has to be taken when FDA says this is the
17 way I want it reported, that FDA also says this is
18 also the way I want dry weight measured; so that we're
19 all on the same basis and we don't have somebody
20 measuring it one way and somebody measuring it
21 another.

22 So it's not to take away from the idea.

1 It's just to point out that that requires a little
2 more complete explanation of what it is you want the
3 person who is doing the testing to do, which normally
4 happens through the Federal Register process and the
5 rest of all that.

6 So I wasn't worried about it. I just
7 pointed it out as something that's not quite so easily
8 done.

9 DR. HATSUKAMI: We also discussed the issue
10 of looking at the constituents per milligram of
11 nicotine for smokeless tobacco products, as well as
12 per unit, which is per a tin of smokeless tobacco.
13 Those are the three methods that we had discussed
14 regarding reporting for smokeless tobacco.

15 Are there any other concerns, comments
16 regarding -- yes, Dr. Burns?

17 DR. BURNS: Just that I don't think those
18 are separate. Each one of them provides information,
19 all of which perhaps need to be necessary in any
20 reporting. For the FDA to make sense out of this
21 information, at a minimum, they need to know
22 concentration per unit something and they also need to

1 know how many units are in the standard use of that
2 particular product.

3 So they're really part of the same thing.

4 So as I thought Cliff was saying, what would make
5 sense would be to have reported the unit dose; that
6 is, how many dry weight grams or whatever is the
7 normal dose of that particular product, and then,
8 also, to have the information on concentration
9 provided in a standard way per gram of something so
10 that one can convert back and forth from this is how
11 concentration exists per amount of tobacco and this is
12 what the dose exists per the use of the product for
13 the individual.

14 DR. HATSUKAMI: Right. I guess the
15 challenge is the unit dose. Jack?

16 DR. HENNINGFIELD: Something that maybe it's
17 so obvious and that's why we haven't mentioned it, but
18 just to make sure it's in the record, is that with
19 smokeless tobacco, especially when we're talking about
20 nicotine, I think it's important that we talk about
21 nicotine actual content and free nicotine.

22 DR. HATSUKAMI: Good point.

1 DR. HENNINGFIELD: Or unprotonated nicotine.

2 DR. HATSUKAMI: So just to go back to the
3 per unit dose, regarding smokeless tobacco, it could
4 be done two ways. One is that the company can decide
5 what that unit dose is or the FDA can make that
6 decision, and I'm not sure if there's any particular
7 recommendation for one or the other.

8 DR. FARONE: Well, not a recommendation, but
9 the point that I think Dr. Burns made before, it's
10 okay, as long as you have the information to inter-
11 convert them.

12 So you'd have to know how many grams in the
13 tin so that then you could do it per gram, because the
14 idea is to have enough information to be able to look
15 at these metrics in different ways that all give you
16 some relative bearing on how things are changing and
17 how these chemicals, these constituents vary from
18 product to product, from time to time.

19 So I think we're all sort of on the same
20 page. We've just got to make sure that the list
21 includes enough information to be able to inter-
22 convert between all of these metrics.

1 DR. HATSUKAMI: Okay. That sounds good.

2 DR. HENNINGFIELD: I guess there are a
3 number of things that maybe we're not mentioning them
4 because they are so obvious. But with over-the-
5 counter drugs, that's another area where there's a lot
6 of experience that FDA has, where actual use studies
7 are done. And it's not just the information you
8 provide, but it's the education that goes along with
9 the information and sometimes the education is
10 sufficient to put on the package; sometimes, also,
11 given in other forms; sometimes marketing type
12 campaigns.

13 So I don't think we can prescribe what
14 should be done, but consumers have to have information
15 to understand the information that they're given.
16 They have to be educated. It cannot stand alone, or
17 consumers are likely to be deceived.

18 DR. HATSUKAMI: That's a good point that you
19 make. Yes, Dr. Burns?

20 DR. BURNS: Let me suggest that I think what
21 we want to do is have the manufacturer provide the
22 unit dose, that is, the dose that is normally used by

1 the individual, with the proviso that the FDA has to
2 review and accept that as being a reasonable
3 approximation of the actual use of the product.

4 That does two things. One, it puts the
5 manufacturer in the position of having to make an
6 assessment based on some evidence of how the product
7 is actually used, which will particularly be important
8 for new products, where the FDA won't have any basis
9 to know how it's used until it's been out on the
10 market for several years.

11 So that puts the manufacturer on notice and
12 it also then gives the FDA the authority, if it feels
13 the information is not reasonable, to either force the
14 manufacturer to go back and provide data to establish
15 that, to force the manufacturer to provide data at the
16 time at which it's initially set, so that they get a
17 reasonable estimate, or to conduct their own
18 evaluation to assess how the product is actually being
19 used in the real world.

20 If the FDA has to set the metric, I'm afraid
21 there will be a very long lag time between changes in
22 the product and changes in what the FDA specifies is

1 the use.

2 DR. HATSUKAMI: Any comments? Jack?

3 DR. HENNINGFIELD: Dr. Burns mentioned that
4 it can take several years, and I think none of us want
5 the light tobacco cigarette experience to be repeated,
6 where it took decades to find out.

7 Without going into mechanisms and tools that
8 FDA has at its disposal, it is clear now that FDA,
9 with pharmaceutical products, sometimes requires
10 quarterly surveillance or annual surveillance, and it
11 depends on the magnitude of the concern, but it can
12 require that. So we don't have to necessarily wait
13 four years.

14 I think the assumption is also that any
15 snapshot in time may not reflect what happens six
16 months later. And so, again, without being
17 prescriptive, the concept that surveillance has to be
18 appropriately sensitive and frequent and geographic to
19 capture problems, and the Tobacco Control Act has the
20 word "surveillance" all over it. So that the concept
21 is already there.

22 I guess maybe, again, that's why we're not

1 discussing it. But anything that involves consumer
2 communication has to be accompanied by that type of
3 surveillance to make sure what happens in the real
4 world is not unexpected and that when unintended
5 consequences occur, which they will, we pick it up
6 quick.

7 DR. BURNS: But wouldn't you agree, Jack,
8 that the burden should be on the manufacturer to
9 define what the unit dose is and to provide the
10 information substantiating that rather than the burden
11 being on the FDA to decide what that dose is?

12 DR. HENNINGFIELD: With pharmaceutical
13 products, that's a condition of marketing and with the
14 FDA making sure that it has appropriate means of
15 verifying and checking, but with the burden being on
16 the manufacturers, again, as a condition of it being
17 allowed to market the product.

18 DR. HATSUKAMI: Dr. Heck?

19 DR. HECK: I think that perhaps some of
20 Jack's concerns here may be allayed by the provisions
21 of the act going forward that requires rather
22 extensive and complete notifications and applications

1 for new product approvals or notifications, petitions
2 for the introduction of substantially equivalent
3 products and things like that.

4 So the FDA will be fully informed on an
5 ongoing basis of changes in product design in a timely
6 or in an advanced fashion. So I would think that at
7 least some of those concerns would be reduced in the
8 future regulatory environment.

9 DR. HATSUKAMI: Okay. So basically, the
10 recommendation that David Burns made is that the
11 manufacturers should be responsible for determining
12 the unit does.

13 Any other further discussions?

14 [No response.]

15 DR. HATSUKAMI: Okay. I just want to
16 clarify, with the cigarettes then, I guess it's pretty
17 much the same issue. We can do it by per stick and
18 per milligram of nicotine. Smoke volume was not
19 considered to be a good measure. So are we in
20 agreement with that?

21 DR. BURNS: With the proviso that the
22 reporting should be per stick.

1 DR. HATSUKAMI: I'm sorry.

2 DR. BURNS: The reporting should be per
3 stick and include tar and nicotine in the reporting.

4 DR. HATSUKAMI: Right.

5 DR. BURNS: Because if you report per
6 milligram tar or per milligram nicotine, you lose the
7 ability to convert into other metrics.

8 DR. HATSUKAMI: Right. That makes sense.

9 DR. BURNS: Or convert reliably.

10 DR. HATSUKAMI: Right. Any other comments
11 on that? Okay. We only have one more question to
12 tackle that was asked of us. And I think that instead
13 of taking a break, should we just forge forward? Then
14 I think we should tackle this question and then we
15 could adjourn.

16 It's the one that says -- it's not that
17 hard. No, I'm sorry, I guess that was the last
18 question. Yes. That's the last question. I'm sorry
19 about that. Okay.

20 Any other further comments? Dr. Husten?

21 DR. HUSTEN: I wonder, do we have the
22 ability to pull up slide 8 from my presentation

1 yesterday? I wanted to go back to the charge to the
2 committee, because I think today we heard some
3 information that you feel would be useful for you to
4 have for the next meeting in order to complete your
5 responsibilities.

6 I wanted to just make sure that we have a
7 comprehensive list, I guess, or what you think you
8 need to complete the work so that we don't come back
9 next time and we've given you the things that we heard
10 and then folks are saying, "Well, we really need this"
11 or "we really need that."

12 So I guess I would like folks to take a
13 minute and think about what information you would like
14 to have by the next meeting so that you can complete
15 the work, because as I had mentioned yesterday, we're
16 asking you to get the work done within the timeframe
17 of the two subcommittee meetings.

18 I think you've made a lot of progress here,
19 but I just wanted to make sure we had a good list of
20 what you wanted for the next meeting before you
21 adjourned.

22 DR. HATSUKAMI: Did anybody take notes in

1 terms of the questions, the information that we wanted
2 for the next meeting?

3 DR. HUSTEN: I have some scattered notes. I
4 know there was one that was what other countries have
5 done regarding the sampling and smoking regimens. And
6 both for the cigarettes and for the smoking, what
7 other countries do in terms of ISO and Canadian
8 intense; what they do in terms of smokeless, in terms
9 of the methods of, I guess, analyzing; the questions
10 about what information other countries have about the
11 variability or what they've already found about the
12 variability around some of these constituents with the
13 methods that they are using.

14 I heard about getting the Massachusetts data
15 on smokeless tobacco as another data source beyond the
16 example list that we had. There was looking at some
17 of the lessons learned around food and around drugs,
18 around some of the issues around portion size or -- I
19 don't remember for the OTC drugs what the exact --

20 DR. TEMPLETON-SOMERS: Actual use.

21 DR. HUSTEN: Actual use. Okay. There was,
22 I think, one thing -- I don't know if it was actually

1 a charge to find it, but there was a suggestion about
2 looking at the -- or asking the industries to provide
3 some of the cross-industry data that they've done
4 looking at each other's products, around whether there
5 was some consistency in terms of -- go ahead.

6 DR. FARONE: I don't think we necessarily
7 have to ask. There were a couple points at which
8 literature regarding that would be useful. They may
9 wish to provide it or we could have somebody look for
10 it.

11 But the idea was when they evaluate each
12 other's samples, which they have done often, and they
13 report that, either within their own stuff or
14 especially if they've made an outside publication on
15 it, that that information would tell us something
16 about the variability that they've experienced with
17 their own methods.

18 The point was, because Dr. Heck made a good
19 point, that some of them show more variability than
20 you can use comfortably. But I was looking the other
21 way. If people make measurements using two or three
22 different methods and they see the same amounts in

1 products, then that would be very useful as one that
2 we know we'd be comfortable, having not a problem with
3 FDA looking at whatever that particular constituent
4 was.

5 So it was a question of getting that
6 information. I guess asking them is one way. Another
7 way is to do a literature search.

8 DR. HUSTEN: Okay. I had looking at EPA and
9 FDA, especially around foods, around acceptable
10 criteria for variability; also, how other countries
11 develop this. The Massachusetts benchmark study was
12 listed as also another piece of information around the
13 variability of the method compared to the variability
14 across products.

15 There was, again, the idea of what do other
16 agencies use around acceptable criteria for
17 regulation, specifically, air and water analyses. And
18 one of our charges was to go back and have the more
19 comprehensive list of the rationale for each of the
20 constituents on the preliminary list.

21 I think there was one about asking the
22 various laboratories whether their lab has a procedure

1 and whether that can be measured commercially; and,
2 also, within that, if a single test can give results
3 on multiple constituents, to note that so we get some
4 sense of the number of tests that might be required,
5 as well as the number of constituents on the list.

6 That's what I had from this afternoon. Did
7 you have some other ones, David?

8 DR. ASHLEY: I have one more, which I don't
9 know if you actually said it or not, but I did have
10 one more. I was checking mine off as you were going
11 through yours.

12 There was one, which was how do other
13 countries sample packs and what's the frequency of the
14 sampling. I don't know if you hit that one or not.

15 DR. HUSTEN: I have that written down, but I
16 didn't say it.

17 DR. HATSUKAMI: Dr. Burns?

18 DR. BURNS: There was the whole request to
19 NIDA to come up with the assessment of metrics of
20 addiction and what information is available on the
21 constituents for those metrics.

22 DR. HATSUKAMI: Dr. Farone?

1 DR. FARONE: Yes. And there was an open
2 part of Dr. Watson's slide that might be instructive
3 for the entire group as to the sample preparations,
4 just different methodologies for sample preparation,
5 just so that could be a backdrop to the information
6 that we would get from these other sources.

7 DR. HATSUKAMI: That was sample preparation
8 for smokeless tobacco or just in general?

9 DR. FARONE: Just in general. He mentioned
10 that it would be deferred until the next meeting and I
11 think it's important, if we're going to be talking
12 about what other countries are doing, to have some,
13 maybe at the beginning, this is what it takes to
14 prepare samples, this number of different ways that
15 it's been done and even how CDC has done it, number of
16 different methods.

17 DR. HUSTEN: So given that list, I guess, is
18 there anything else that people think they might --
19 yes.

20 DR. HECK: One thing to add to your list,
21 Dr. Husten. It's been mentioned several times by Dr.
22 Watson and, indeed, in some written comments and

1 verbal, the ongoing CORESTA efforts to standardize
2 methods in conjunction with ISO, but also independent
3 and preceding the ISO -- ISO does have -- there are
4 standard methods for sampling and things like that.

5 Let's be sure we have that in our inventory
6 of resources and informational sources. And there are
7 some accompanying publications by Purkis and others in
8 recent literature that will give us some insight into
9 some of the elements required for this sort of
10 analysis.

11 DR. HATSUKAMI: Any other additional
12 information? I think, in large part, the information
13 that we'll obtain will help us determine what should
14 be the constituents associated with addiction, but
15 also help to answer some of the issues that you have
16 brought up-to-date for us, the committee, to address.

17 But, also, there may be additional issues
18 that, obviously, you want the committee to address at
19 the next meeting, too, that we're real clear on, and
20 so we don't know what kind of information or
21 recommendation to provide.

22 DR. BURNS: And it might be wise to send the

1 list of things out by e-mail to everybody in the next
2 day or two so that as people recover from the excesses
3 of the last day or two, they have a clearer thought
4 process that they can remember all the things that
5 were requested.

6 DR. HUSTEN: So you're saying send the list
7 of what information you thought you need or send the
8 preliminary list so that you have that sort of --

9 DR. BURNS: Certainly, send the preliminary
10 list, but I was thinking more of there are all these
11 requests for information that we have made, you may
12 not have that complete list. There may be some
13 nuances of it that may have been missed.

14 It would be, I think, helpful to send that
15 out to the committee in the next day or two and they
16 can provide you feedback about whether you got it
17 actually right or whether --

18 DR. HUSTEN: You can do clarifying. And
19 I'll leave this to the DFO, I'm not sure individuals
20 can suggest other --

21 DR. TEMPLETON-SOMERS: Yes. We'll have
22 problems doing that and maintaining the rules of FACA.

1 So your background will be coming pretty soon.

2 DR. BURNS: I'm happy to do whatever you
3 like. I was just thinking in terms of making sure
4 that what was said actually gets reflected in the
5 list; not having the opportunity to add to that list,
6 but rather to make sure that the things that were
7 recommended were actually what made it to the list.

8 DR. TEMPLETON-SOMERS: We'll do what we can.

9 DR. HATSUKAMI: Any other comments before we
10 adjourn? Well, I certainly wanted to thank the
11 committee for all the efforts that they had put into
12 their deliberations. I think we've done some very
13 important work here today. So I thank you for your
14 thoughtfulness in doing this.

15 I would also like to thank the CDC and FDA
16 for their presentations to help us in our
17 deliberations. Thank you very much, and we'll see you
18 -- Dr. Ashley?

19 DR. ASHLEY: Before we adjourn, I do have a
20 few things to say before you use the word "adjourn."
21 First off, I personally want to thank everybody for
22 their participation, for the time you spent here.

1 There were some very worthwhile discussions.
2 I think we made some tremendous progress. I am very,
3 very pleased with how things went and for the things
4 that were discussed. There are some hard questions
5 and I think there was some very good discussion in
6 addressing those questions, and that was really very,
7 very good.

8 Input from scientific experts is really
9 going to be critical in maintaining the science-driven
10 process that the Center for Tobacco Products is moving
11 forward with, and that input from experts like you is
12 going to really be critical in us formulating the
13 specifics of how we carry out the statute.

14 Advisory committees and subcommittees are
15 really an integral part of accomplishing that mission
16 of CTP, and I thank you very much for your work there.

17 Thanks a lot for remaining focused. I think
18 you did a great job in really addressing the questions
19 that were posed to you.

20 I want to myself give a special thanks to
21 Patricia Richter, who did a tremendous amount of work
22 in preparation for this. And I also very, very much

1 want to thank the staff of the Center for Tobacco
2 Products, who worked long hours and through lunch and
3 at all times here and did a great job in pulling
4 information together in a very quick time.

5 For me personally, that was quite
6 impressive. I've been on the job now for 2.5 days and
7 to see this staff and what they can do is just
8 incredible to me. I'm actually more excited than when
9 I started the other day. So I personally want to
10 thank them for their dedication and their hard work
11 and for their ability to pull things together very,
12 very quickly.

13 So thank you all for being here and
14 participating in this process.

15 DR. HATSUKAMI: Okay. I think we are
16 adjourned now, and we'll see you sometime in July.

17 [Whereupon, at 2:28 p.m., the meeting was
18 adjourned.]

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